MEDICAL LIBRARY

VOL. 188, No. 1. JULY, 1934 No. 748

JUL 5 1934

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

CLINICAL OBSERVATIONS ON AORTIC STENOSIS. By SYLVESTER McGINN and PAUL D. WHITE 1

INTRAVENOUS INJECTION OF METHYLENE BLUE IN MAN WITH REFERENCE TO ITS TOXIC SYMPTOMS AND EFFECT ON THE ELECTROCARDIOGRAM. By J. ERNEST NADLER, M.D., HENRY GREEN, B.S., and ARTHUR ROSENBAUM, B.S. . . . 15

THE THERAPEUTIC EFFICACY OF BISMUTH SUBNITRATE IN ARTERIAL HYPERTENSION. By CURTIS BRUEN, M.D. 21

THE IONTOPHORESIS OF ACETYL-BETA-METHYLCHOLIN CHLORID IN THE TREATMENT OF CHRONIC ARTHRITIS AND PERIPHERAL VASCULAR DISEASE. PRELIMINARY REPORT. By JOSEPH KOVACS, M.D. 32

THE BONE MARROW IN IDIOPATHIC THROMBOPENIC PURPURA. By JOHN S. LAWRENCE and RALPH E. KNUTTI 37

MEGAKARYOCYTOSIS IN WHITE MICE WITH SPONTANEOUS MAMMARY CARCINOMAS. By W. C. HUEPER 41

LEUKOCYTOSIS AFTER PARENTEARL INJECTION OF LIVER EXTRACT. By OVID O. MEYER, M.D., WILLIAM S. MIDDLETON, M.D., and ETHEL M. THEWLIS . . . 49

SURGICAL ASPECTS OF PERNICIOUS ANEMIA WITH SPECIAL REFERENCE TO THE TREATMENT. By R. G. HAHN, M.D. 60

THE RELATION BETWEEN ORAL AND RECTAL TEMPERATURES IN NORMAL AND SCHIZOPHRENIC SUBJECTS. By HUGH T. CARMICHAEL, M.D., C.M., M.S., and FORREST E. LINDER, PH.D. 68

INSULIN THERAPY IN TUBERCULOSIS. By ANDREW L. BANYAI, M.D., and GEORGE H. JURGENS, M.D. 76

THE CINCHOPHEN OXIDATION TEST OF LIVER FUNCTION IN PULMONARY TUBERCULOSIS. By JOHN B. O'CONNOR, B.A., HERBERT YOUNG, M.D., JOHN STEIDL, M.D., and FRED H. HEISE, M.D. 81

GAUCHER'S DISEASE. REPORT OF A CASE WITH PRESENTATION OF A TABLE DIFFERENTIATING THE LIPOID DISTURBANCES. By AARON CAPPER, M.D., HERMAN EPSTEIN, M.D., and ROBERT A. SCHLESS, M.D. 84

ARTHRITIS, ANABOLIC NUTRITION AND HEALTH. A STUDY OF THE NOURISHMENT AND HEALTH OF JOINTS. By FRANCIS LOWELL BURNETT, M.D., and FRANK ROBERTS OBER, M.D. 93

A SURVEY OF HUMAN INTESTINAL PROTOZOAN PARASITES IN PHILADELPHIA. By H. CORWIN HINSHAW, PH.D., M.D., and ETHEL M. SHOWERS, R.N. 108

THE AGE-INCIDENCE RELATIONS IN DIABETES MELLITUS. By GREGORY PINCUS, SC.D., ELLIOTT P. JOSLIN, M.D., and PRISCILLA WHITE, M.D. 116

THE PRESENT STATUS OF THE DIAGNOSTIC INTRADERMAL TEST FOR HUMAN TRICHINIASIS. By RICHARD D. FRIEDLANDER, M.D. 121

INDEX TO PHYSICIAN'S SUPPLIES . . ADV. PAGE 34

Contents Continued on page x

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1934, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR.

To your patients

your prescription is the embodiment of your experience and skill in the treatment of disease

YOU, *in turn,* depend upon the pharmacist to follow implicitly your directions. Any failure on his part to dispense what is ordered may nullify the expected results and impair the patient's confidence in your medication.

When Luminal is specified in your prescription, there is no valid excuse for the substitution of something else. The name serves to identify the original product which has gained a prominent place as a sedative, antispasmodic and hypnotic in the treatment of various nervous and other diseases.

Hundreds of published clinical reports testify to its therapeutic efficiency while high and uniform chemical purity is assured by years of experience in its manufacture. Your prescription for Luminal is therefore well founded.

LUMINAL

Reg. U. S. Pat. Off. & Canada
Brand of PHENOBARBITAL

WINTHROP CHEMICAL COMPANY, INC., NEW YORK, N.Y.

285 M

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1934

ORIGINAL ARTICLES.

CLINICAL OBSERVATIONS ON AORTIC STENOSIS.*

By Sylvester McGinn,

ASSISTANT IN MEDICINE, MASSACHUSETTS GENERAL HOSPITAL,

AND

Paul D. White,

PHYSICIAN, MASSACHUSETTS GENERAL HOSPITAL; ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON.

(From the Cardiographic and Pathologic Laboratories of the Massachusetts General Hospital.)

Although lesions of the aortic valve including "calcareous disease" have been recognized for centuries, little interest has been exhibited in the important clinical condition of aortic stenosis until recently. Over 250 years ago Rayger reported, in 1672, the sudden death of a man whose heart showed an "osseous fusion" of the aortic cusps (quoted by Bonet[3] in 1679), and later, in 1706, Cowper[7] described 3 cases having petrifaction of the stenosed semilunar valves of the left ventricle. During the next two centuries occasional references, usually brief, were made to the pathology and clinical aspects of aortic stenosis. Finally, to complete the pathologic picture, Mönckeberg,[12] in 1904, described the histology of the aortic cusps and noted atherosclerotic changes at their bases which when present in an extreme degree would produce aortic stenosis.

The etiology of many cases of aortic stenosis has remained in doubt as is illustrated in an extreme degree by 10 patients under 25 years of age reported by Gallavardin,[9] having the clinical evidence of this lesion but which he thought were neither rheumatic, arteriosclerotic, nor congenital in origin. That aortic stenosis occurs not infrequently in rheumatic heart disease is well known but opinions vary as to the etiology of the calcareous type of the valve lesions. Christian[5] believed chronic rheumatic endocarditis underlying the process to be highly probable, while Libman discussing Christian's paper expressed the viewpoint that the condition may also be superimposed on congenital

* Presented in brief before the American Clinical and Climatologic Association, Washington, D. C., May 9, 1933.

bicuspid valves, on valves previously affected by subacute bacterial endocarditis, and that it may occur in pure atherosclerosis. Margolis, Ziellessen, and Barnes[11] have thought that some cases represent the result of a non-inflammatory degenerative process, and Clawson, Bell, and Hartzell,[6] following the observations of Mönckeberg, likewise expressed the belief that certain cases have a non-inflammatory origin. Tuohy and Eckman[14] have reported 3 cases with calcareous changes in the aortic valve which, in the absence of a rheumatic history, they thought were best explained by Mönckeberg's theory. Anitschkow[1] has described, in addition to inflammatory valvular changes, an atherosclerosis of the valves with lipoid deposits in the middle fibroelastic layers and without cicatricial deformity. In a third group he included those valves with combined inflammatory and atherosclerotic changes in which lipoids replace cicatricial tissue wherever it is found and later undergo calcareous changes resulting in greatly deformed valves.

There are thus certain aspects of aortic stenosis that still require study. These are especially its etiology and frequency, the comparison of those cases showing calcareous change in the aortic valve with those showing no calcareous change, and a comparison of instances of aortic valve stenosis alone with those having associated lesions of the mitral valve. We are presenting herewith statistical data of interest bearing on these points.

Our own material for study has been obtained from a review of 6800 postmortem examinations made at this hospital and from 4800 clinical cardiovascular cases seen in private practice. The criteria in selecting the cases depended in the postmortem series on the statement of the pathologist that the aortic valve was stenosed or on his description indicating that there was a contraction of the valve, and in the clinical series on evidence presented by the patient sufficient to make a definite diagnosis of aortic stenosis.

The requirements stated to be necessary for establishing the clinical diagnosis of aortic stenosis have in the last two generations approached the extremes, with the consequent tendency first to overdiagnose and then later to underdiagnose the condition. The idea of a generation ago that a basal systolic murmur alone permitted the diagnosis of aortic stenosis resulted in the lesion being reported too frequently on clinical examination. The more recent extreme point of view has minimized the frequency of the lesion and may be considered to be overcautious in requiring the following criteria to be present before permitting the diagnosis of aortic stenosis: (1) loud aortic systolic murmur; (2) aortic systolic thrill; (3) absent aortic second sound; (4) plateau or anacrotic pulse; and by some (5) an aortic diastolic murmur. Our experience has indicated that a diagnostic criterion midway between these views is preferable. The diagnosis of aortic stenosis may at times be justified in the presence of a harsh and loud aortic systolic murmur transmitted to the neck, whether or not it be accompanied by one or all of the signs of a confirmatory nature such as an aortic thrill, absent aortic second sound, a plateau pulse, and aortic diastolic murmur; in the presence of evidence of other valvular deformities or of a history of rheumatic infection, and in the absence of evidence of luetic aortitis or of marked hypertension, a loud systolic murmur heard in the second right interspace should strongly suggest stenosis of the aortic valve.

Incidence of Aortic Stenosis. The frequent occurrence of aortic stenosis seems to be confined to certain geographic areas as is indicated by statistical surveys on cardiovascular disease and by personal communications. From the latter and from the data of Davison and Thoroughman[8] concerning heart disease in the negro race, we may assume that aortic stenosis is a rare condition in the southern section of our country. Norris[13] found 48 cases of aortic stenosis in a series of 9940 patients (0.4%) showing cardiac lesions at postmortem examinations in two Philadelphia hospitals. The studies of Boas,[2] Christian,[5] Clawson,[6] Margolis,[11] and their associates show that aortic valve disease with stenosis is not uncommon in the northern states. Campbell and Shackle[4] writing in England observed that out of every 6 rheumatic cases 1 had aortic stenosis and insufficiency without mitral stenosis and 1 had aortic stenosis and insufficiency with mitral stenosis. Grant[10] studied 1000 English ex-service men with signs of acquired cardiovascular disease and has recently reported his findings after 10 years of observation. In this group, there were 43 persons who, he believed, had aortic stenosis and regurgitation without mitral stenosis and 6 others who had both aortic stenosis and regurgitation with mitral stenosis.

In our own series of 6800 postmortem cases of all types of disease, there were 123 cases of aortic stenosis (1.8%) and in the clinical group of 4800 cardiovascular patients there were 113 cases (2.3%). There were 37 additional patients in the clinical group who had suggestive but not conclusive signs of aortic stenosis; these questionable cases were not included in this analysis. In the postmortem series, mitral stenosis occurred in 159 cases, coëxisting with aortic stenosis in 50 hearts; and in the clinical series there were 434 cases of mitral stenosis, being associated with aortic stenosis 40 times.

The incidence of mitral stenosis in our two groups was 2.3% and 9.2%, as compared to 1.8 and 2.3% for aortic stenosis.

The incidence of aortic stenosis was higher than we had expected since it occurred twice in about every 100 autopsies in the routine postmortem series and in about 3 of every 100 patients with cardiovascular trouble in the clinical series. The relatively close relationship in frequency of mitral stenosis to aortic stenosis was interesting, it being nearly 1 to 1 in the first series and in a ratio of 4 to 1 in the second; moreover, in the postmortem group about every third case of mitral stenosis had a coëxisting aortic stenosis while in the clinical group the ratio was thought to be lower, 1 in every 11 cases. How much of this discrepancy may be due to the more careful routine clinical search for mitral stenosis, which is the rule, than for aortic stenosis, how much to the possibility that the slighter grades of aortic stenosis may produce less clear clinical evidence than the slighter grades of mitral stenosis, and how much to the possibility that the more marked degrees of aortic stenosis are less common than the more marked degrees of mitral stenosis we do not as yet know;

the last mentioned possibility we are investigating further. The discrepancy will undoubtedly be somewhat diminished when aortic stenosis is more zealously searched for, as is indicated by the fact that in the second half of the clinical series twice as many cases were discovered as in the first half of the series. It is of interest to note that the aortic stenosis demonstrated at autopsy was diagnosed clinically in only one-third of the cases. We are as yet much more often missing aortic stenosis when it is present than diagnosing the condition when it is absent.

Etiology of Aortic Stenosis. A definite history of the rheumatic infection was obtained in 23% of the autopsied cases and in 46% of the clinical series; the latter series included another 32% with a questionable rheumatic history. The relative frequency of aortic stenosis in association with mitral stenosis and with a positive rheumatic history in New England is striking.

The presence of important intercurrent infections in the history was noted in about one-third of the postmortem cases and in nearly half of the clinical cases, which incidence probably varies but little from that in the population at large. Those infections most frequently recorded were tonsillitis, pneumonia, influenza, typhoid fever, and gonorrhea in the order named, the majority occurring before the age of 40. It has seemed to us likely that a severe tonsillitis with or without peritonsillar abscess in youth or middle age may be, more than the other infections just named, an etiologic factor in the origin of aortic valve disease found in middle life or old age without mitral valve disease and without a history of rheumatic fever; we have encountered non-syphilitic aortic regurgitation in several such cases developing in males of middle age. Syphilis was not diagnosed in any case of our clinical series and in only 4 cases of our postmortem series; of the postmortem series 54 had had their Wassermann reactions tested and in only 3 were they positive. The diagnosis of subacute bacterial endocarditis was made on 6 occasions in the clinical series but was found only twice in the postmortem series.

There were 16 cases out of the total 123 autopsied (13%) which should be judged on gross examination to be Mönckeberg's sclerosis of the aortic valve although microscopic sections of the cusps were not available. None of these cases had a positive history of a rheumatic infection. We encountered no cases of congenital aortic stenosis or subaortic stenosis in our postmortem series nor, so far as we can tell, in our clinical series.

The current opinion that aortic stenosis is primarily an affliction of males and that it is consistent with longevity is substantiated by our figures. In the postmortem series 87 (71%) of the 123 cases were males, and 71 (63%) of the 113 clinical cases were of the male sex. In these same series respectively 56 (46%) and 65 (58%) of the patients lived to be 50 or over. The known duration of the

lesion, as well as could be determined for the postmortem cases, was 9.5 years and for the clinical cases 12.7 years up to the present time or until the time of their death.

Symptoms and Signs of Aortic Stenosis. The complaints of the patients were chiefly those of congestive failure, including dyspnea, orthopnea and edema, and were found mostly in the histories of the autopsied patients where the diagnosis of congestive failure had been most frequent. Faintness, dizziness, or actual syncope were also fairly common complaints, having been noted in 22% of the histories of the combined series of 236 cases. Angina pectoris was found in 47 patients (19%) and cardiac asthma in 36 patients (15%).

The clinical diagnosis of aortic insufficiency in our cases of aortic stenosis was made frequently in both series; clinically diagnosable aortic insufficiency was present in 52 of the cases coming to autopsy and in 74 cases of the clinical series. All of our clinical cases of aortic stenosis had loud systolic murmurs at the base of the heart, almost all of which were accompanied by systolic thrills. A basal systolic murmur was recorded in ½ the patients of the postmortem group and a basal systolic thrill in ¼; the physical examination very often showed a harsh systolic murmur transmitted all over the precordium, which was frequently attributed antemortem to a mitral lesion. The records contain a few observations as to the wide transmission of the systolic murmurs to neck and back. The aortic second sound was either diminished in comparison with the pulmonary second sound or entirely absent in a majority of the patients, this finding being more common in the autopsied series where the cases of congestive failure were also more numerous. Not rarely, however, the aortic second sound was found to persist even in the presence of well-marked aortic stenosis, later proved at postmortem examination.

The pulse was described as normal or full in the majority of the patients, a Corrigan pulse being noted in 12 cases of the entire series of postmortem and clinical cases; a plateau pulse was reported in 9.

The systolic blood pressure was found to be 150 mm. of mercury or over in 65 patients (of the total of 236 of both groups) of which 28 were in the postmortem group and 37 were in the clinical group. The blood pressure was above 200 mm. of mercury systolic in 10 patients, of which number 8 belonged to the clinical series. The majority of diastolic pressures varied between 80 and 110 mm. mercury. The average pulse pressure was 60 mm., unexpectedly high.

Auricular fibrillation was diagnosed in 62 of the total of 236 cases, being present most frequently in patients having mitral stenosis also.

Only 10 of the total number of cases failed to show cardiac

enlargement to the left by either percussion or roentgenogram. Infrequently the calcified aortic valves could be seen in fluoroscopic examination and rarely they could be demonstrated by teleroentgenography (7-foot heart films).

Electrocardiograms were taken on 78 patients of the clinical series and on 32 of those of the postmortem series. Left axis deviation was the most common finding, right axis deviation being present in a few cases with mitral stenosis; there was no abnormal axis deviation in others. Various types of delayed conduction were found in 22 of the 110 tracings, there being 6 with full bundle-branch block, 8 with lesser intraventricular block, and 8 with auriculoventricular block. Abnormal *T* waves exclusive of the bundle-branch-block cases were seen in 66 of the 110 electrocardiograms.

Of the 172 patients known to be dead out of the total of 236 cases of both series, 12 patients died following operations and 9 others died suddenly; the large majority died in congestive failure. The average duration of the terminal illness was 4.3 months and the average number of attacks of congestive failure was two.

Pathologic Anatomy. The pathologic findings in the 123 cases of the postmortem series indicate the infrequency of syphilis with aortic stenosis, only 2 cases of luetic aortitis having been found and in 1 of these there was also a marked rheumatic endocarditis with mitral stenosis. A microscopic section of an aortic cusp in 1 case contained many easily demonstrable Treponemata pallida. A congenitally bicuspid aortic valve was found with the aortic stenosis on 4 occasions, there being only 6 of these congenital lesions recorded in the 6800 autopsies. Subacute bacterial endocarditis was found at autopsy in 2 of the 123 cases, an active endocarditis of other nature in 9, and a chronic rheumatic endocarditis was reported by the pathologist as definite in 18 cases. Additional pathologic data will be given with the comparisons of the various conditions.

A Comparison of Cases of Calcareous and of Non-calcareous Aortic Stenosis (Table 1). Of the 123 cases in the postmortem series, 86 had calcareous changes in the aortic valve, whereas less than half that number (that is, the balance of 37 cases) had aortic stenosis without calcareous changes. The males outnumbered the females in the calcareous group 4 to 1, but the sex distribution was about equal in the smaller non-calcareous group. In relatively few cases did males have aortic stenosis without some evidence of calcareous change. The majority (60%) of the patients with calcareous aortic stenosis were over 50, whereas only 4 of the 37 patients with non-calcareous aortic stenosis were over 50. This indicates that aortic stenosis is consistent with longevity and that aortic valvular calcification is to be expected in aortic stenosis with increasing years. Old age, however, is not the only factor behind the calcareous changes in the cusps, inasmuch as 34 patients (40%) with such changes died before they were 50 years old. This is to be

compared with the finding that 33 (89%) of the 37 cases who showed non-calcareous aortic stenosis died before 50.

TABLE 1.—CASES OF AORTIC STENOSIS IN 6800 AUTOPSIES.

	Calcareous.			Non-calcareous.			Total.
	With a rheumatic history.	Without a rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	Total.	
Number	32	54	86	24	13	37	123
Sex—Male	27	42	69	12	6	18	87
Female	5	12	17	12	7	19	36
Under 50 years of age	17	17	34	24	9	33	67
Over 50 years of age	15	37	52	0	4	4	56
Intercurrent infections	16	25	41	3	3	6	47
Aortic insufficiency (clinical diagnosis)	17	16	33	15	4	19	52
Aortic stenosis (clinical diagnosis)	12	16	28	10	3	13	41
Dyspnea	30	42	72	22	7	29	101
Cardiac asthma	8	11	19	0	0	0	19
Angina pectoris	6	9	15	0	1	1	16
Blood pressures, 150 mm. or over	6	16	22	3	3	6	28
Pulse pressures, average in mm.	53	58	56	73	44	66	59
Auricular fibrillation	12	11	23	13	3	16	39
Wassermann positive, 54 taken	1	1	2	1	0	1	3
Subacute bacterial endocarditis	0	0	0	1	1	2	2
Duration terminal illness (months)	4.2	5.0	4.6	2.5	6.0	3.5	4.3
Heart weight average in gm.	696	572	616	639	467	579	605
Number over 500 gm.	26	37	63	17	7	24	87
Calcareous changes in mitral valve	17	18	35	5	2	7	42
Coronary sclerosis	8	31	39	2	2	4	43
Aortic sclerosis	12	35	47	3	2	5	52
Fusion of cusps into a ring	21	38	59	15	6	21	80
Bicuspid arrangement	6	16	22	3	5	8	30

A rheumatic history was obtained from about ⅓ of the patients in the calcareous group. It is of interest to note that only 15 of the total of 56 patients of the postmortem series who lived to be over 50 had a clear history of rheumatic infection. The history of intercurrent infections, however, was distinctly more common in these older cases of the calcareous group than in those of the non-calcareous group, the frequency being 47 and 12% respectively. All of 10 cases with a history of gonorrhea and 9 of 12 cases with a history of pneumonia were in the series of cases having calcareous changes. Subacute bacterial endocarditis was present in only 2 of the total postmortem series of 123 cases and both had non-calcareous aortic valve lesions. There were two definite congenital bicuspid aortic valves in each group, calcareous and non-calcareous.

All of the 16 definite cases of Mönckeberg's sclerosis belong, of

course in the calcareous group but the majority of instances of calcareous deposits were found in cases without definite indication of primary Mönckeberg's sclerosis (70 in all), *i. e.*, in the rheumatic cases and in other cases of unknown etiology.

Dyspnea and, to a lesser extent, edema were commonly found in both groups. All of the cases of cardiac asthma were found in the calcareous group as were all of the cases of angina pectoris except one. The older age of the calcareous group was undoubtedly of importance in this respect. Syncope and dizziness were complained of equally in both groups. There was practically no difference in the two groups in the known duration of the terminal illness or in the number of attacks of congestive failure suffered by the patients but the calcareous group was known to have had the lesion 1.5 years longer on the average than had the other group.

The clinical diagnosis of aortic stenosis was correctly made in about $\frac{1}{3}$ of each group. Aortic insufficiency was diagnosed clinically in both groups, slightly more often than was aortic stenosis itself, being reported in half of the non-calcareous patients and in 38% of the calcareous. The systolic blood pressure was elevated above 150 mm. mercury more often in the calcareous group; 25% as compared with 16% of the other patients. All of the 8 patients having a diastolic pressure over 110 mm. mercury belonged with the calcareous cases. The pulse pressure was higher than we had expected in both groups with an average of 56 mm. in the calcareous and 66 mm. in the non-calcareous.

The radial arteries were noted to be tortuous, thickened, or sclerotic on 40 occasions, 38 of these being in patients with calcareous aortic valve changes, that is, in the older cases. Auricular fibrillation occurred less frequently in this group (26%) than in the non-calcareous (43%), whereas premature contractions were found about equally in both groups. Among the few instances showing disturbance of conduction by electrocardiogram, bundle-branch block and intraventricular block predominated in the calcareous cases, but only 1 of the 3 cases with auriculoventricular block belonged in that group.

The heart weights were similar in the two groups, averaging 616 gm. in the calcareous group, with 75% above 500 gm., and averaging 579 gm. in the non-calcareous group, with 63% weighing more than 500 gm. Atherosclerotic changes in the aorta and coronary arteries and calcareous involvement of the myocardium and the mitral valve were much more frequent in the older calcareous group. Infarcts of the spleen, lungs, and kidneys occurred in that order and with the same relative frequency in both groups.

Whether or not calcareous changes are present in the aortic valve is relatively unimportant as compared with the condition of aortic stenosis itself, inasmuch as it is the latter which is the factor producing the clinical signs and causing the secondary changes

in the heart. The degree of aortic stenosis may be considerably increased, however, by the deposition of masses of calcium salts and the presence of these may be helpful in establishing the diagnosis of aortic stenosis by fluoroscopic examination or by the 7-foot heart film as a result of the recent improvement of Roentgen ray technique.

A Comparison of Cases with Aortic Stenosis Alone and of Cases with Aortic Stenosis in Association with Other Valve Lesions (Tables 2 and 3). This resolves itself chiefly into a discussion of

TABLE 2.—AORTIC STENOSIS, 4800 CLINICAL CARDIOVASCULAR CASES (15 CASES WITH A NON-STENOTIC LESION OF THE MITRAL VALVE NOT SUMMARIZED).

	Aortic stenosis alone.				Aortic stenosis and mitral stenosis.				Total.
	With a rheumatic history.	Without a rheumatic history.	With a questionable rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	With a questionable rheumatic history.	Total.	
Number	16	23	19	58	29	0	11	40	98
Sex—Males	10	14	12	36	17	0	7	24	60
Females	6	9	7	22	12	0	4	16	38
Age, average in years	50.2	67.8	49.4	56.9	44.4	0	47.2	45.1	52.0
Males, average in years	55.6	69.4	45.5	57.5	46.8	0	47.9	47.2	53.4
Females, average in years	41.3	65.4	56.2	56.0	40.9	0	46.0	42.1	50.0
50 years and over	8	23	11	42	8	0	4	12	54
Aortic insufficiency, clin. diag.	12	6	8	26	29	0	9	38	64
Known duration of lesion in yrs.	14.1	5.4	12.5	10.2	17.8	0	11.1	16.1	13.7
Intercurrent infections	6	6	12	24	17	0	4	21	45
Subacute bact. endocarditis	0	0	1	1	3	0	1	4	5
Dyspnea	12	10	12	34	20	0	7	27	61
Cardiac asthma	2	4	6	12	2	0	2	4	16
Angina pectoris	7	14	4	25	3	0	2	5	30
Edema	2	4	4	10	13	0	3	16	26
Syncope	6	10	5	21	6	0	4	10	31
Well developed and nourished	12	20	16	48	16	0	7	23	71
Auricular fibrillation	1	0	4	5	9	0	5	14	19
Blood pressures, 150 mm. or over	7	14	4	25	7	0	1	8	33
Pulse pressures, average in mm.	63	80	42	61	67	0	49	62	62
With cardiac enlargement	16	23	19	58	28	0	11	39	97
Electrocardiograms L. A. D.*	7	12	8	27	8	0	5	13	40
Bundle branch block	1	0	0	1	1	0	1	2	3
A–V block	1	1	0	2	1	0	0	1	3
Intraventricular block	2	1	0	3	1	0	0	1	4
Number of electrocardiograms	13	18	12	43	17	0	9	26	69

* L. A. D. = Abnormal degree of left axis deviation.

aortic stenosis with and without mitral stenosis. A third group of cases having aortic stenosis in combination with a non-stenosing mitral valve lesion is so closely aligned to the solitary aortic lesion in most respects that these two groups may be considered practically as one. This third group is composed of those cases having slight fibrosis or thickening of the mitral valve and also of those cases in which there are calcareous changes in the mitral leaflets without stenosis of the valve.

Of the 123 autopsied cases of aortic stenosis, there were 50 in which mitral stenosis coëxisted. As has been previously stated with

regard to the total number of autopsies every third case of mitral stenosis had an associated aortic stenosis. There were 36 females in the entire postmortem series of aortic stenosis and 21 of these were in the group having combined lesions of mitral stenosis and aortic stenosis. The majority of the 67 patients dying before the age of 50 showed stenosis of both valves, the mortality before that age for the individual groups being 78% for the combined lesions and 38% for the aortic stenosis alone.

TABLE 3.—CASES OF AORTIC STENOSIS ALONE AND IN ASSOCIATION WITH OTHER VALVE LESIONS (POSTMORTEM SERIES).

	Aortic stenosis alone.			Aortic stenosis and mitral stenosis.			Aortic stenosis and a non-stenotic mitral lesion.			Total
	With a rheumatic history.	Without a rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	Total	With a rheumatic history.	Without a rheumatic history.	Total	
Number	9	26	35	37	13	50	10	28	38	123
Sex—Male	8	20	28	21	8	29	10	20	30	87
Female	1	6	7	16	5	21	0	8	8	36
Under 50 years of age	7	12	19	29	10	39	5	4	9	67
Over 50 years of age	2	14	16	8	3	11	5	24	29	56
Intercurrent infections	3	6	9	6	6	12	7	7	14	35
Aortic insufficiency, clin. diag.	3	11	14	23	4	27	6	5	11	52
Aortic stenosis, clin. diag.	2	10	12	17	2	19	3	7	10	41
Dyspnea	6	17	23	36	12	48	10	20	30	101
Cardiac asthma	1	2	3	4	1	5	3	8	11	19
Angina pectoris	3	7	10	2	0	2	1	3	4	16
Edema	8	15	23	31	9	40	9	17	26	89
Blood pressures, 150 mm. or over	2	8	10	4	2	6	3	9	12	28
Pulse pressures, average in mm.	85	57	63	66	32	59	52	62	60	61
Auricular fibrillation	0	5	5	24	2	26	1	7	8	39
Wassermann positive, 54 taken	1	1	2	1	0	1	0	0	0	3
Subacute bacterial endocarditis	1	0	1	0	0	0	0	1	1	2
Duration terminal illness (months)	3.2	5.0	4.5	3.6	6.8	4.3	3.0	4.0	3.6	4.3
Heart weight average in gm.	627	582	593	622	567	592	883	541	631	605
Number over 500 gm.	6	17	23	27	9	36	10	18	28	87
Calcareous changes in mitral valve	0	0	0	16	7	23	6	13	19	42
Coronary sclerosis	3	11	14	6	3	9	1	19	20	43
Aortic sclerosis	3	15	18	8	3	11	4	19	23	52
Fusion of cusps into a ring	2	13	15	29	11	40	5	20	25	80
Bicuspid arrangement	6	11	17	3	1	4	0	9	9	30

Most of the patients (74%) having mitral and aortic stenosis together had a positive rheumatic history as compared with 26% in the group with aortic stenosis alone. Excepting for tonsillitis the patients having aortic stenosis and mitral stenosis were relatively free from other intercurrent infections such as gonorrhea, influenza and pneumonia.

The symptoms and signs of congestive failure, namely orthopnea, dyspnea and edema, were nearly the same in incidence in both groups, but the frequency of cardiac asthma, angina pectoris, dizziness, and syncope was greater in the patients having aortic stenosis alone. The known length of time that the patient had

aortic valve involvement was less than the average for the entire series when mitral stenosis coëxisted with the aortic stenosis; this same group with combined valve lesions tended to have more attacks of congestive failure.

The clinical diagnosis of aortic stenosis was made correctly in the same proportion in both groups of the postmortem series. In that series aortic insufficiency was noted clinically in 54% of the patients having both aortic and mitral stenosis; this number represents more than half of the total cases with aortic regurgitation in the postmortem series. The difference in the systolic blood pressures of the two groups was not striking; it was found to be over 150 mm. in 48% of the patients with mitral and aortic stenosis as compared with 61% of those with aortic stenosis alone. The average pulse pressures were similar in the two groups. There was a distinct difference in the frequency of auricular fibrillation, which occurred in only 17% of the cases with aortic stenosis alone and in 52% of the group with both aortic and mitral stenosis.

The average heart weights were approximately the same in both groups, with a like number in each weighing more than 500 gm. Sclerosis of the coronary arteries and of the aorta was more common in the group with aortic stenosis alone. There were 42 cases in which calcification was found in the mitral valve; 23 of this number were included in the cases with both aortic and mitral stenosis.

It was found that 24 of the group of 50 cases showing both aortic and mitral stenosis also had calcareous changes in the aortic valve. Two aortic cusps were found to be fused, giving a bicuspid arrangement of the valve on 30 occasions in the whole postmortem series; only 4 of these had an associated mitral stenosis.

Cases with Varying Degrees of Aortic Stenosis. Believing that the degree of stenosis of the aortic valve would be an important factor in determining the clinical signs and the pathologic changes, we have compared three groups of cases having aortic stenosis of varying amount. There are 15 cases in each of the three groups, all of which had calcareous aortic stenosis demonstrated at the postmortem examination and which did not have mitral stenosis. The first group of cases had marked aortic stenosis with calcification but without clinical evidence of insufficiency. Although aortic regurgitation undoubtedly was present to some extent, it was not sufficient to give the usual auscultatory findings. The second group includes those cases of moderate aortic stenosis caused by calcareous deposits at the base of the cusps, which were not accompanied by clinical aortic insufficiency. In the third series of 15 cases, in addition to considerable aortic stenosis all had the clinical signs of aortic insufficiency or the lesion was such that the pathologist thought that it necessarily was present in at least moderate degree.

In the second group, which had only moderate stenosis of the

aortic valve, not 1 case had the discharge diagnosis of aortic stenosis made clinically. This does not indicate, however, that signs and symptoms were not produced by these changes, inasmuch as at least 8 of the 15 cases had records of systolic murmurs heard at the base of the heart, accompanied in 1 case by a thrill. Despite this available evidence attention was not directed toward stenosis of the aortic valve. Congestive failure, as shown by the history of dyspnea and the finding of edema, was very infrequent in this group, edema occurring but once. The aortic second sound was louder than the pulmonary second sound in a greater number of patients of this group than in the other two groups.

TABLE 4.—CASES OF AORTIC STENOSIS OF VARYING DEGREES IN THE POSTMORTEM SERIES.

	Marked calcareous aortic stenosis without clinical insufficiency.	Moderate aortic stenosis with calcareous deposits chiefly at base of cusps without clinical insufficiency.	Calcareous aortic stenosis with marked clinical or pathologic insufficiency.
Number	15	15	15
Sex—Male	11	11	14
Female	4	4	1
Under 50 years of age	2	2	7
Over 50 years of age	13	13	8
Rheumatic fever history	3	1	4
Intercurrent infections	7	7	8
Aortic stenosis, clinical diagnosis	3	0	12
Dyspnea	14	5	15
Cardiac asthma	3	2	3
Angina pectoris	5	3	7
Edema	11	1	14
Blood pressures, 150 mm. or over	6	9	3
Pulse pressures, average in mm.	42	81	52
Auricular fibrillation	1	3	2
Duration terminal illness (months)	4.6	5.8	3.5
Heart weight, average in gm.	588	450	683
Number over 500 gm.	10	5	13
Calcareous changes in mitral valve	7	5	2
Coronary sclerosis	9	10	10
Aortic sclerosis	13	12	11
Fusion of cusps into ring	8	2	10
Bicuspid arrangement	7	2	5

The sex distribution was approximately the same for all three groups, with the males predominating 3 to 1. Of the 15 patients having free aortic insufficiency (Group 3), 7 died before the age of 50 as compared with 2 dying before this age in each of the other two groups. Moreover, the average duration of the terminal illness was slightly shorter for this group than for the other two, and the incidence of angina pectoris was greater. These findings indicate that the presence of free aortic insufficiency with aortic stenosis adds a greater burden on the heart and makes the prognosis less favorable.

The systolic blood pressures were found to be over 150 mm. mercury more frequently in the second group, namely that with

only moderate stenosis, while the third group, that with marked aortic regurgitation, had the fewest pressures above 150 mm. mercury. The average pulse pressure of the patients of the second group, with calcareous changes at the base of the cusps, was 81 mm., of those with aortic insufficiency 52 mm., and of those with marked aortic stenosis but without much aortic insufficiency 42 mm.

The pathologic observations indicate that those hearts in which aortic stenosis was complicated by enough insufficiency to reveal itself clinically were the largest, weighing an average of 683 gm. This compares with the average weights of 588 gm. for the group having marked stenosis and of 450 gm. for the hearts with moderate stenosis. The frequency of sclerosis of the aorta and coronary arteries was equivalent in all three groups. Involvement of the mitral valve by extension of the calcareous process downward from the aortic valve was seen in only 2 cases having marked aortic insufficiency. With the slighter extent of the calcification and deformity of the aortic valve in the group having moderate stenosis only 4 cases were found with the cusps fused into a ring or having a bicuspid arrangement.

Summary and Conclusions. 1. A study of aortic stenosis is presented herewith, based on 123 cases proved at postmortem examination among 6800 necropsies of patients with all types of disease at the Massachusetts General Hospital and 113 clinical cases among 4800 patients studied by us in cardiovascular consultation practice. In the postmortem series 71% of the patients were males and in the clinical series 63%.

2. Aortic stenosis occurred in the postmortem series almost as often as did mitral stenosis. The lower incidence in our clinical series may be due in part to the fact that it is difficult or impossible clinically to diagnose aortic stenosis if the stenosis is but slight in degree. Closer search for the lesion resulted in our finding clinically twice as many cases of aortic stenosis, definite or questionable, in the second half of the clinical series as in the first half. It appears justifiable to make the clinical diagnosis of aortic stenosis when a loud harsh systolic murmur is heard in the region of the second right intercostal space and is transmitted to the neck, in the absence of pronounced aortic dilatation due to luetic aortitis or marked hypertension, especially when there is evidence of other valvular deformity or a history of rheumatic infection. An aortic systolic thrill, a diminished or absent second aortic sound, a plateau pulse, and an aortic diastolic murmur are important confirmatory findings, but it is not necessary to await the presence of all of these signs before making the diagnosis; if we do await all these signs we shall miss a large majority of cases of aortic stenosis often of considerable clinical importance.

3. A comparison has been made, in the postmortem series, of cases showing calcareous changes in the stenosed aortic valve with

cases showing no calcareous change in the valve. Calcareous valvular changes were found more frequently than non-calcareous (86 to 37), with males predominating and living past middle life in the calcareous group while the sexes were evenly distributed in the non-calcareous group, few of whom lived longer than 50 years. Angina pectoris, cardiac asthma, and higher blood pressures were more frequently found in the calcareous group while a positive rheumatic history and auricular fibrillation were more frequent in the non-calcareous group. The average pulse pressures were approximately the same. The heart weights were similar in the two groups but calcareous changes in the mitral valve, aorta, and coronary arteries were much more common, as would be expected, in the older, calcareous group. The presence or absence of calcareous changes in the aortic cusps is clinically relatively unimportant as compared to the aortic stenosis itself, excepting as it alters the degree of stenosis or aids in the Roentgen ray diagnosis.

4. A comparison of the autopsied cases having aortic stenosis alone with those having aortic stenosis combined with mitral stenosis showed males to be represented equally in both groups; females, however, were three times more frequent in the combined than in the isolated group. Mitral stenosis was found much more often in the cases dying under 50, while aortic stenosis alone occurred most commonly in people beyond that age. Angina pectoris was found more often in patients with aortic stenosis alone (14 to 2), while auricular fibrillation occurred much more often in cases with complicating mitral stenosis (26 to 13). The average heart weights were approximately the same for the two groups (612 gm. and 592 gm.). Coronary sclerosis and aortic sclerosis were more common in cases of aortic stenosis alone; sclerotic changes in the mitral valve were found in 23 of the 50 cases with complicating mitral stenosis.

5. In three groups of patients of the postmortem series having various degrees of calcareous aortic stenosis, it was found that the correct diagnosis had not been made clinically in any having only moderate calcareous changes, mostly at the base of the aortic cusps, and that the symptoms of congestive failure were less frequent in this group than in those instances where the lesion was more marked. At least a few of the cases showing only moderate aortic stenosis should have been diagnosed correctly antemortem if proper attention had been directed to the signs that were present. The patients with pronounced aortic insufficiency in addition to aortic stenosis had a shorter terminal illness and died at a younger age than did the cases where stenosis of the valve predominated. The average weight of the hearts in the group with pronounced aortic insufficiency was also higher, the smallest hearts being found in those cases with little or no aortic insufficiency and with only a moderate amount of stenosis.

6. It is evident from this analysis that all grades of aortic stenosis exist, much as in the case of mitral stenosis; that aortic stenosis

even of considerable degree is common, particularly in males; that it is doubtless often caused by infection, especially rheumatism; that calcareous changes are found chiefly in the older patients, no matter what the cause; that aortic stenosis is less serious than aortic regurgitation of high degree, being found in many old patients after years of valvular disease;* that it is sometimes associated with considerable hypertension; that, as in the case of mitral stenosis, the symptoms and signs vary in number and degree with the extent of the aortic stenosis; that aortic stenosis is often overlooked when it should be clinically diagnosed; and that it is an important lesion to search for, even in the lesser grades, because of the progression of the lesion and of the frequency with which it is associated with congestive heart failure.

BIBLIOGRAPHY.

1. Anitschkow, N.: Libman Anniv. Vol., **1**, 65, 1932.
2. Boas, E. P.: Med. Clin. North America, **6**, 613, 1922.
3. Bonet, T.: Sepulchretum sive Anatomica Practica, Geneva, Cramer and Perachon, **1**, 891, 1700; 1st ed., 1679.
4. Campbell, M., and Shackle, J. W.: Brit. Med. J., **1**, 328, 1932.
5. Christian, H. A.: Trans. Assn. Am. Phys., 1931, **46**, 96, and J. Am. Med. Assn., **97**, 158, 1931.
6. Clawson, B. J., Bell, E. T., and Hartzell, T. B.: Am. J. Path., **2**, 223, 1926.
7. Cowper, W.: Phil. Trans., London, **24**, 1970, 1706.
8. Davison, H. M., and Thoroughman, J. C.: Southern Med. J., **21**, 464, 1928.
9. Gallavardin, L.: Presse méd., **29**, 224, 1921.
10. Grant, R. T.: Heart, **16**, 275, 1933.
11. Margolis, H. M., Ziellessen, F. O., and Barnes, A. R.: Am. Heart J., **6**, 349, 1931.
12. Mönckeberg, J. G.: Virchow's Arch. f. pathol. Anat. u. Physiol. u. f. klin. Med., **172**, 472, 1904.
13. Norris, G. W., and Landis, H. R. M.: Diseases of the Chest and the Principles of Physical Diagnosis, 3d ed., Phila. and London, W. B. Saunders Company, 1927.
14. Tuohy, E. L., and Eckman, P. F.: Minn. Med., **14**, 289, 1931.

INTRAVENOUS INJECTION OF METHYLENE BLUE IN MAN WITH REFERENCE TO ITS TOXIC SYMPTOMS AND EFFECT ON THE ELECTROCARDIOGRAM.

By J. Ernest Nadler, M.D.,

ASSISTANT IN MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY, CLINICAL ASSISTANT VISITING PHYSICIAN, BELLEVUE HOSPITAL.

Henry Green, B.S.,

AND

Arthur Rosenbaum, B.S.,

NEW YORK.

(From the Therapeutics Laboratory, University and Bellevue Hospital Medical College, New York University.)

Considerable attention has been recently aroused concerning the intravenous injection of methylene blue. At the moment, the

* It is of interest that a few years ago when we searched our records for long-lived patients with heart disease one of the lesions which we failed to find persisting from youth to old age was aortic regurgitation of high degree.

greatest interest centers about its clinical use in the treatment of cyanide,[1] and carbon monoxide poisoning.[1d, 1e, 1f, 1g, 1i, 1j, 2] In these conditions, however, no altogether acceptable proof has been furnished of its value.[3] Its use has also been suggested in cases of methemoglobinemia.[4]

Standard textbooks on the physiologic action of drugs give practically no definite information concerning the action of methylene blue in the body. Although Marshall,[5] working with malaria, found that as much as 400 gr. (26 gm.) may be given by mouth over several weeks without any toxic symptoms, it has been generally observed that large doses may produce gastric irritation and painful micturition. No mention can be found in the literature of any harmful or untoward effects from intravenous use of this dye; in fact one is led to believe that no more care than usually attends an intravenous injection of saline need be taken. This may be accounted for when it is realized that the patients are usually in coma and on the verge of death at the time the drug is administered. In view of the fact that no study has been made of the effect of intravenous injection of methylene blue in normal man, and that it is both desirable and necessary in order to better understand its action in pathologic conditions, we undertook its investigation.

Material and Method. Eighteen normal adults, who volunteered for this study, were given 50 cc. of a 1% solution of methylene blue intravenously, average therapeutic dose recommended.[1h] One per cent solution of Methylthionine chlorid, U. S. P. was made by dissolving 1 gm. of the drug[6] in 100 cc. of hot physiologic saline. It was stirred with a glass rod, filtered, sterilized, and stored in a dark closet for 24 hrs. before using. No attempt was made to dry the salt. The inevitable presence of very small percentages of reductant methylene white[7] was disregarded.

The speed of the intravenous injection varied in different cases from 5 to 30 min. usually about 10 min. for 50 cc. Two individuals received 3 injections and 3 received 2 injections of the drug. As we found that it took from 3 to 5 days for the dye to be eliminated, a second injection was not given until the dye of the previous injection was no longer present in the body. All subjects had electrocardiograms taken before, during and for some time after the injection of methylene blue, in 1 case Leads I and III were taken simultaneously.

In 6 cases the hemoglobin and methemoglobin values of the blood were ascertained by the method of van Slyke and Hiller.[8] The only variation from their technique was that the CO was drawn directly from the storage bottle into the mixing chamber of the van Slyke manometric apparatus through a thick-walled capillary pipette fitted with a stopcock and a rubber tip instead of using a Hempel pipette. In collecting the samples of blood, special care was taken to prevent contamination with methylene blue.

Effects. No report of the electrocardiographic changes following the injection of methylene blue in man could be found in the literature. Schott[9] injected methylene blue intravenously in dogs and failed to find any striking or permanent changes. He obtained a decrease in the *R* wave, while the *T* wave was increased in ampli-

tude. In man we found that the effect on the *T* wave was just the opposite (Fig. 1). In every instance the *T* wave showed a great reduction in height, frequently became isoelectric and occasionally even negative. The *R* wave also usually showed a decrease in height. Recovery was usually complete within 2 hr. after the injection.

The point of action is apparently not vagal, as found by Cook[10] in isolated heart preparations, for no marked change in heart rate

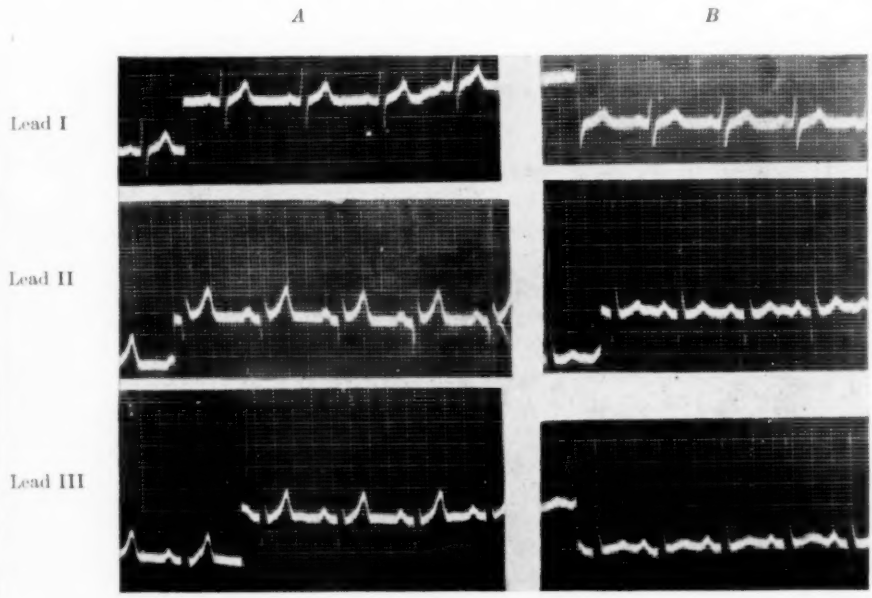


FIG. 1.—Case 18. *A*, control. *B*, shortly after injection of 50 cc. of 1% methylene blue, showing the depression of the *T* wave. At *B* there was 0.83 gm. % methemoglobin with a loss of 7.1% hemoglobin.

was noted. Likewise, methylene blue does not appear to attack the automatic and conductive tissues directly, since no definite changes were found in the *P–R* or *Q–R–S* interval, nor were *A–V* block, bundle-branch block or irregularities in rhythm found. Our observations indicate that methylene blue may have a direct action on the ventricular musculature.

There was usually a slight increase in respiratory rate and a sense of oppression in the chest, with some difficulty in breathing. Occasionally there was a dull pain over the heart. No appreciable rise or fall in blood pressure was observed. A moderate acceleration of the heart rate was present, similar to that observed by Stammers[11] in dogs.

Soon after starting the injection the skin and mucous membranes became bluish. Restlessness, apprehension and fine fibrillary tre-

mors of the face and extremities developed. A sense of "burning" in the mouth and warmth in the stomach was always present and this was occasionally accompanied by nausea and vomiting. When vomiting occurred the gastric contents were found to be stained blue. The saliva was also tinted blue, corroborating the findings of Rembridge, Hanke, and Halpert[12] that methylene blue is secreted by the stomach and salivary glands as well as by the liver[13] and kidneys. Abdominal pain was occasionally noted.

A number of subjects became excited by the injection: in one case the pupils dilated and the individual had a feeling of impending death; in another, at the height of the injection, everything went black before his eyes and he started to perspire profusely. One individual, more apprehensive than usual at the start of the injection, complained of severe pain in the chest with a feeling of weight on the sternum; became very excited and, owing to the symptoms of impending collapse, the injection was stopped at 25 cc. Paresthesias were noted as an early complaint in every case. A number of individuals complained of slight nausea, dizziness, headache, and mental confusion for about 12 hr. following the injection. These effects have been entirely temporary and without any serious result.

Dr. Norman Jolliffe of the Psychiatric Division of Bellevue Hospital was kind enough to allow us to refer to a patient who was admitted in a psychotic condition following the use of O_2 and CO_2 by inhalation and an intravenous injection of methylene blue for carbon monoxide poisoning. The patient was restless, noisy, had to be restrained in a straight jacket and was disoriented as to time and place. She remained mentally confused and hyperactive for about 4 days. It was the impression of the Psychiatric Staff that this condition was a result of methylene blue poisoning.

Most of the drug is eliminated by the kidneys and it usually required from 3 to 5 days for the dye to be eliminated by this route. Urine containing methylene blue is irritating and excites frequency, burning, and painful micturition. Two individuals complained of severe burning in the scrotum and groin before the injection of 50 cc. of methylene blue was completed.

Untoward effects at the site of injection similar to those obtained with arsphenamin may result if the injection is made in part into the sheath or subcutaneous tissue.

Discussion. At first sight it would seem that the picture presented could be explained as due entirely to anoxemia, as it is well known that methylene blue produces methemoglobin.[1m, 1p, 14] Certain observations are, however, distinctly opposed to such a view. Although we are not in a position to know how great a reduction in hemoglobin would be necessary to produce such a clinical picture if it were due to anoxemia, we do know that Haldane, Makgill and Mavrogordato[15] found that as much as 6% of the blood pigment in rabbits could be changed to methemoglobin without producing any symptoms. Furthermore, Dautrebande[16] found no significant

change in cardiac output until the hemoglobin approached 50%, and Harrison and Blalock[17] until blood amounting to about 3% of the body weight of the dog had been lost. The maximum loss of hemoglobin that we found at the height of the symptoms was only 8.3% of the total hemoglobin (Table 1), and in 2 cases, in which the symptoms and electrocardiographic changes were of the usual magnitude, the decrease was negligible (0.6 and 0.4%). We are therefore led to conclude that the observed decrease in hemoglobin is not proportional to the intensity of the symptoms.

Although the number of cases studied permits only a qualitative interpretation of the data, it is evident that the magnitude of change in the $Fe{+}{+} \rightarrow Fe{+}{+}{+}$ system is too slight to consider it responsible for the clinical picture obtained, unless it be argued that the reversibility of this reaction is almost immediate. If the condition which we have described was due to methemoglobinemia, it would hardly seem possible that the blood taken at the height of the symptoms would not show more methemoglobin (Table 1). However, Stadie[18]

TABLE 1.—AMOUNT OF METHEMOGLOBIN FORMED AND PER CENT LOSS OF HEMOGLOBIN FOLLOWING THE INJECTION OF 50 CC. OF A 1% SOLUTION OF METHYLENE BLUE.

Case.	Hemoglobin control, Gr. %.	Decrease in hemoglobin after injection, Gr. %.	Methemoglobin present after injection, Gr. %.	Loss of hemoglobin expressed as % of total hemoglobin.
12	15.7	1.0	0.7	6.4
14	12.8	0.8	1.3	6.0
15	14.3	1.2	1.3	8.3
16	13.0	0.1*	0.9	0.6
17	11.7	0.1*	0.7	0.4
18	13.4	1.0	0.8	7.1

* Within limit of experimental error which was equivalent to 0.1 gr. %.

says that methemoglobin is destroyed rapidly in the circulating blood, but that when 30 to 50% of the total hemoglobin is changed suddenly following intravenous injections of sodium nitrite, methemoglobin may be found in the blood. Therefore, the possibility of demonstrating methemoglobin in clinical cases would seem slight and may account for the negative results reported by Geiger[14] and the relatively small amounts found in our cases.

Furthermore, the clinical picture is not truly comparable to the one found in anoxemia. If this condition were brought about by acute anoxemia, a more marked effect on respiration and circulation[19,20] than what we found would certainly be expected. Lewis and Matheson[21] found that heart block occurred regularly during acute anoxemia in cats and dogs. Although Kountz and Gruber,[22] Ward and Wright[19] and Greene and Gilbert[20] in their electrocardiographic studies found a decrease in amplitude of the *T* wave during moderate anoxemia, similar to our observations with methylene blue, in our cases, as we have shown, anoxemia played nowhere near so important a rôle as it did in theirs. We are led to conclude that the harmful effects of methylene blue should not be associated

essentially or chiefly with methemoglobin, but rather attributed to disorders of function due to the direct action of the drug itself.

Conclusions. 1. Our observations indicate that methylene blue, under the conditions of this study, has two actions. The first of these is the oxidation of hemoglobin to methemoglobin. The amount of methemoglobin found immediately following the injection of the average therapeutic dose is small.

2. The second is that this drug, used intravenously, excites the individual and by its rapid elimination into the stomach and urine produces transitory gastro-intestinal and urinary irritation. The most frequent toxic symptoms observed were restlessness, paresthesias, a sense of "burning" in the mouth and stomach, pain in the chest and strangury. These manifestations usually subsided in 24 to 48 hours. Leakage of a small amount of methylene blue about the vein gives rise to a very painful infiltration.

3. Electrocardiographic studies show that methylene blue produces a reduction in the height or even reversal of the *T* wave frequently with lowering of the *R* wave. This suggests depression of the ventricular musculature.

4. The amount of methemoglobin found and the subsequent decrease in hemoglobin is not of sufficient magnitude to account for the clinical picture described on the basis of anoxemia.

5. We therefore wish to point out that the indiscriminate use of methylene blue may produce unpleasant results and be dangerous to the patient.

We are indebted to Dr. Arthur C. DeGraff for valuable suggestions in connection with this work.

REFERENCES.

1*a*. Sahlin, B.: Ueber den Antagonismus zwischen Methylenblau und Cyankalium, Skandinav. Arch. f. Physiol., 1926, **47**, 284. *b*. Eddy, N. B.: Antagonism between Methylene Blue and Sodium Cyanide, J. Pharmacol. and Exp. Therap., 1930, **39**, 271. *c*. Eddy, N. B.: Regulation of Respiration. The Antagonism between Methylene Blue and Sodium Cyanide, Ibid., 1931, **41**, 449. *d*. Brooks, M. M.: Effect of Methylene Blue on CN and CO Poisoning, Proc. Soc. Exp. Biol. and Med., 1932, **29**, 1228. *e*. Brooks, M. M.: The Effect of Methylene Blue on HCN and CO Poisoning, Am. J. Physiol., 1932, **102**, 145. *f*. Brooks, M. M.: Methylene Blue as Antidote for Cyanid and Carbon Monoxid Poisoning, J. Am. Med. Assn., 1933, **100**, 59. *g*. Brooks, M. M.: Methylene Blue as an Antidote to Carbon Monoxid Poisoning, Am. J. Physiol., 1933, **104**, 139. *h*. Geiger, J. C.: Cyanid Poisoning in San Francisco, J. Am. Med. Assn., 1932, **99**, 1944. *i*. Geiger, J. C.: Methylene Blue as Antidote for Cyanid and Carbon Monoxid Poisoning, Ibid., 1933, **100**, 59. *j*. Geiger, J. C.: Methylene Blue Solutions in the Treatment of Carbon Monoxid Poisoning, Ibid., p. 1103. *k*. Geiger, J. C.: Methylene Blue Solutions in Potassium Cyanid Poisoning, Ibid., 1933, **101**, 269. *l*. Wendel, W. B.: Methylene Blue and Cyanid Poisoning, Ibid., 1933, **100**, 1054. *m*. Wendel, W. B.: The Mechanism of the Action of Methylene Blue and Sodium Nitrite in Cyanid Poisoning, Proc. Am. Soc. Biol. Chem., 1933, *p.c.* *n*. Hanzlik, P. J.: Methylene Blue as Antidote for Cyanid Poisoning, J. Am. Med. Assn., 1933, **100**, 357. *o*. Hug, E.: l'Intoxication par l'acide cyanhydrique. Les substances méthémoglobinisantes comme antidotes de l'intoxication cyanhydrique, Compt. rend. Soc. de biol., 1933, **112**, 511. *p*. Hug, E.: Treatment of Hydrocyanic Acid Poisoning, J. Am. Med. Assn., 1933, **100**, 1621. *q*. Chen, K. K., Rose, C. S., and Clowes, G. H. A.: Amyl Nitrite and Cyanid Poisoning, Ibid., p. 1920.

2*a*. Bell, M. A.: Methylene Blue in Carbon Monoxid Poisoning, Ibid., p. 1402. *b*. Nass, J.: Treatment of a Case of Illuminating Gas Poisoning with Methylene

Blue Solution, Ibid., p. 1862. *c.* Christopherson, A. W.: Report of Cases of Carbon Monoxid Poisoning Treated by Methylene Blue Injection, Ibid., p. 2008.

3. Haggard, H. W., and Greenberg, L. A.: Methylene Blue: A Synergist, not an Antidote, for Carbon Monoxid, Ibid., p. 2001. Trautman, J. A.: Methylene Blue in the Treatment of HCN Gas Poisoning, Pub. Health Rep., 1933, **48**, 1443.

4. Steele, C. W., and Spink, W. W.: Methylene Blue in the Treatment of Poisoning Associated with Methemoglobinemia, New England J. Med., 1933, **208**, 1152.

5. Marshall, D. G.: The "Toxicity" of Methylene Blue, Lancet, 1920, **198**, 1334.

6. Manufactured by National Anilin and Chemical Company.

7. Clark, W. M.: Reduction Potentials of Mixtures of Indigo and Indigo White, and of mixtures of Methylene Blue and Methylene White, J. Wash. Acad. Sci., 1920, **10**, 225. Harvey, E. N.: Further Studies on the Inhibition of Cypridina Luminescence by Light, with Some Observations on Methylene Blue, J. Gen. Physiol., 1926, **10**, 103.

8. Van Slyke, D. D., and Hiller, A. E.: Gasometric Determination of Hemoglobin by CO Capacity Method, J. Biol. Chem., 1928, **78**, 807. Van Slyke, D. D., and Hiller, A. E.: Gasometric Determination of Methemoglobin, Ibid., 1929, **84**, 205.

9. Schott, E.: Ueber experimentelle Beeinflüssung der Form des Elektrokardiogramms. Die Veränderung der Form des Elektrokardiogramms unter der Wirkung von Säure, Alkali und Methylenblau, Deutsch. Arch. f. klin. Med., 1926, **152**, 287.

10. Cook, R. P.: The Antagonism of Acetylcholine by Methylene Blue, J. Physiol. 1926, **62**, 160.

11. Stammérs, A. D.: Effect of Light on Some Physiologic Processes. Action of Methylene Blue, Eosin and Erythrosin on Body Temperature, Blood Pressure and Isolated Heart, So. African J. Sci., 1929, **26**, 519.

12. Rembridge, A. G., Hanke, M. T., and Halpert, B.: Further Observations on the Function of the Gall Bladder. Experiments with Methylene Blue on the Dog. Am. J. Physiol., 1930, **95**, 511.

13. Halpert, B., and Hanke, M. T.: Observations on the Function of the Gall Bladder. Experiments with Methylene Blue on Rabbits, Ibid., 1929, **88**, 351.

14. Neill, J. M.: Studies on the Oxidation of Hemoglobin and Methemoglobin, J. Exp. Med., 1925, **41**, 299.

15. Haldane, J., Makgill, R. H., and Mavrogordato, A. E.: The Action as Poisons of Nitrites and Other Physiologically Related Substances, J. Physiol., 1897, **21**, 160.

16. Dautrebande, L.: Blood Output by the Heart in Anemia, Compt. rend. Soc. de biol., 1925, **93**, 1029.

17. Harrison, T. R., and Blalock, A.: Oxygen Lack and Cardiac Output, J. Am. Med. Assn., 1926, **87**, 1984.

18. Stadie, W. C.: Studies on Blood Changes in Pneumococcus Infections. An Experimental Study of the Formation and Fate of Methemoglobin in the Blood, J. Exp. Med., 1921, **33**, 627.

19. Ward, G. E. S., and Wright, S.: An Electrocardiographic Study of the Human Heart During and After Nitrous Oxid Anesthesia, Lancet, 1929, **2**, 1184.

20. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension, Arch. Int. Med., 1921, **27**, 517.

21. Lewis, T., and Matheson, G. C.: Auriculo-ventricular Heart Block as a Result of Asphyxia, Heart, 1910–1911, **2**, 47.

22. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, Proc. Soc. Exp. Biol. and Med., 1929, **27**, 170.

THE THERAPEUTIC EFFICACY OF BISMUTH SUBNITRATE IN ARTERIAL HYPERTENSION.

By Curtis Bruen, M.D.,
NEW YORK.

(Experiment carried out in the Adult Cardiac Clinics of Beth Israel Hospital and the Hospital for Joint Diseases.)

Adequate control in the investigation of therapeutic results in arterial hypertension, as has been emphasized by Ayman,[1,3] requires

an adequate regulated period of pre-treatment observation, uniform clinical conditions during control and experimental periods, and the determination of the effect of non-specific therapy. These provisions are necessary in order to estimate the spontaneous lability of the blood-pressure, and the effects on the blood-pressure of the experimental procedure. The effects of such factors as frequency of visits, rest periods, and non-specific medication can be individually determined in separate experiments, and subsequently allowed for in interpreting the apparent results of therapy. Both the spontaneous variability of the blood-pressure in response to uncontrolled environmental, physical and psychic conditions apart from clinical observations, and the response incidental to the special conditions of controlled experiment, under which the effect of therapy is to be investigated, can thus be preliminarily determined, and corrected for in the final interpretation of therapeutic results. But this leaves it still necessary to evaluate the change occurring during an experimental period by inference from remote changes which occurred during control periods. Unrecognized adventitious factors may intervene to invalidate such inferences.

Experimental Method. Yet it is possible so to organize the experimental procedure that the chemistry of the experimental and non-specific medications alone differentiates control periods from experimental periods. A standardized procedure for determining the blood-pressure, uniform frequency of visits during control and experimental periods, and the effect of non-specific therapy can be provided for. Only two variables, apart from the long-time trend which may be neglected, remain: adventitious influences and therapeutic actions. Their effects can readily be distinguished. By alternating control periods under non-specific medication, not sensibly different from the experimental medication, with experimental periods under experimental medication, any alteration in the blood-pressure, which occurs during a period of experimental medication, can be referred either to adventitious factors or to the medication according to its continuance or cessation upon the resumption of non-specific medication. Such a procedure makes possible the prosecution of vigorously controlled experimentation on the effects of therapeutic agents in arterial hypertension.

Bismuth subnitrate by mouth has been utilized in dosages up to gr. x, 3 times a day, in the treatment of arterial hypertension by Stieglitz,[2] who, in summarizing his results in extensive, though inadequately controlled, series, reported that the average systolic and diastolic pressures reverted far toward the maximum normals for the average age. In a smaller series, in which control factors were allowed for, Ayman[3] found bismuth subnitrate in such dosage to be without demonstrable effect on the blood-pressure.

Bismuth subnitrate by mouth was found in extensive tests on a subject with normal arterial tension to produce prolonged and

effective reduction of the blood-pressure.[4] Bismuth subnitrate by mouth, by reason of its presumptive nitrite action, would therefore appear to merit adequately controlled application in arterial hypertension to definitively evaluate its therapeutic efficcy. An experimental procedure appropriate to this purpose was elaborated.

Method. The standardized method for determining the blood-pressure consisted in making and recording on a specially designed chart (Chart I) 10 successive readings at each visit. This procedure was regarded as more applicable and practical than the use of rest periods, since it conforms more closely to ordinary clinical usage, can be more uniformly employed and consistently regulated, and requires less psychic adaptation and compliance of the patient. While each reading was being charted the air was allowed to escape freely from the cuff in order that distal circulation might be reëstablished. The time of beginning and concluding each determination was recorded to the nearest half minute. The interval covered by a blood-pressure determination was $3\frac{1}{2}$ or 4 min. in most instances, but ranged from $2\frac{1}{2}$ to $5\frac{1}{2}$ min., depending upon immediate manipulative requirements, and particularly the height of the systolic pressure.

Only blood-pressure determinations made at weekly intervals were regarded as significant and comparable. The respective clinics were held early Monday and Wednesday evenings, with the exception of three Tuesday mornings at one and a Tuesday evening at the other, to avoid greater derangement, or interruption, of the experimental routine by holidays. The patients were seen in turn after variable waiting periods, the length of which depended upon immediate clinical exigencies; but, since the individual patients tended to habituate themselves to coming each week at the same hour, they tended to be seen regularly at about the same time and after uniform waiting periods. At each visit a detailed interval history was taken and a physical examination done in accordance with the standard record-form used in the clinics. The patients were seen exclusively by one physician, who urged the necessity of regular weekly visits, listened with patiently sympathetic interest to all complaints and unburdenings, and evinced a candidly encouraging attitude in responding to inquiries regarding clinical progress.

During a 3-weekly-visit foreperiod, the patients were kept on the lactose-tablet placebo regularly used as control medication in the clinics, in order to permit of comparison of the blood-pressure determinations made according to the special method of the experiment with the blood-pressures recorded during previous observation, and to render the period of previous observation available as a supplementary control period.

Subsequently 3-weekly-visit control periods on non-specific medication consisting of cerium oxalate in amounts grossly equivalent to the prospective dosages of the experimental medication were alternated with 3-weekly-visit experimental periods on bismuth subnitrate. Cerium oxalate was chosen as the non-specific medication, because it is an inert substance having only inert impurities, and in consistency and appearance superficially resembles bismuth subnitrate. Cerium oxalate proved adequate as the control medication inasmuch as but one patient more or less consistently inquired of the occurrence or discontinuance of a slight seeming pinkness and sweetness in the medication after it had in fact been changed, and only one other intimated at one time that she had made a comparison of a left-over sample of a past medication with the present medication and noted a difference.

Three successive experimental courses in which the graded dosages of cerium oxalate of gr. vii, gr. xv, and gr. xxii corresponded to the graded dosage of bismuth subnitrate of gr. x, gr. xx, and gr. xxx were prosecuted.

The medication was dispensed in boxes containing the exact number of powders to be taken before the succeeding visit. The powders were prescribed to be taken 3 times a day, apportioned approximately every 8 hrs. to conduce to an even distribution through the 24 hrs. The hour of the last medication before each visit was asked and recorded to encourage the regular taking of the medication, to insure medication before visits, and to define the interval between the last medication and the registration of its possible effect. This interval ranged from 3 to 6 hrs., but was usually 4 hrs.

Material. Patients newly assigned or carried under the diagnosis of hypertension, unselected except with regard to their maintenance of cardiac compensation and regular sinus rhythm, were entered into the experimental series as they became available. All who proved amenable to the experimental routine were retained, except those who registered diastolic pressures regularly below 90, or who were eliminated through the development of heart failure or prolonged intercurrent illness. The final series (Table 1) consisted of 20 cases, 1 male, 19 females, in 15 of whom all 3 experimental courses were completed, in 3 the first 2 courses, and in 2 only the first course. Two were new patients; 5 were in the first 6 months, and 5 in the second 6 months of observation; 3 were in the second, 3 in the third, and 2 in the fourth year of observation.

Their age ranged from 27 to 73 with a median of 51 years. The stated known duration of hypertension ranged from a few months to 19 years with a median of 3 years. Their average control systolic/diastolic pressure ranged from the minimum of 139/97 to the maximum of 258/137 with a median of 164½/113. The changes in their

LEGENDS FOR CHARTS I AND II.

CHART I.—Blood-pressure record chart. The section to the left of the double line reproduces the blood-pressure readings recorded during the period of previous observation. The mode of the 10 successive blood-pressure readings recorded on each visit during the experiment, indicated by being enclosed in a circle, represents the result of the determination. The medication taken during the interval preceding the visit, together with the time of taking the last dose, and the date, together with the times of beginning and completing the blood-pressure determination, are recorded below the blood-pressure readings. In the subsection on the extreme right, the blood-pressure before and after the inhalation of amyl nitrite is recorded.

CHART II.—Graphic case records. The ordinates represent the blood-pressure in millimeters of mercury; the abscissæ represent successive visits. Each of the 20 large rectangles represent the course of the blood-pressure in the case designated by the number in its upper right-hand corner. Weekly visits during the period of previous observation are indicated by black dots, fortnightly by circles, other visits by circles with numerals subscribed to designate the number of weeks. When, during the period of previous observation, more than one blood-pressure reading was recorded at a visit, the first reading is indicated by being included in the graph of the trend. For the period of the experiment, each level of the blood-pressure recorded in the 10 successive readings of a determination is indicated by a circle, and their mode by a black dot. The trends of the maximum, modal, and minimum pressures are indicated by graphs. The small empty rectangles indicate dosages of cerium oxalate, the blackened rectangles dosages of bismuth subnitrate. Gaps in these rectangles indicate interruption of medication and extensions of the interval between visits. The arrow-tipped vertical lines represent the response to the inhalation of amyl nitrite.

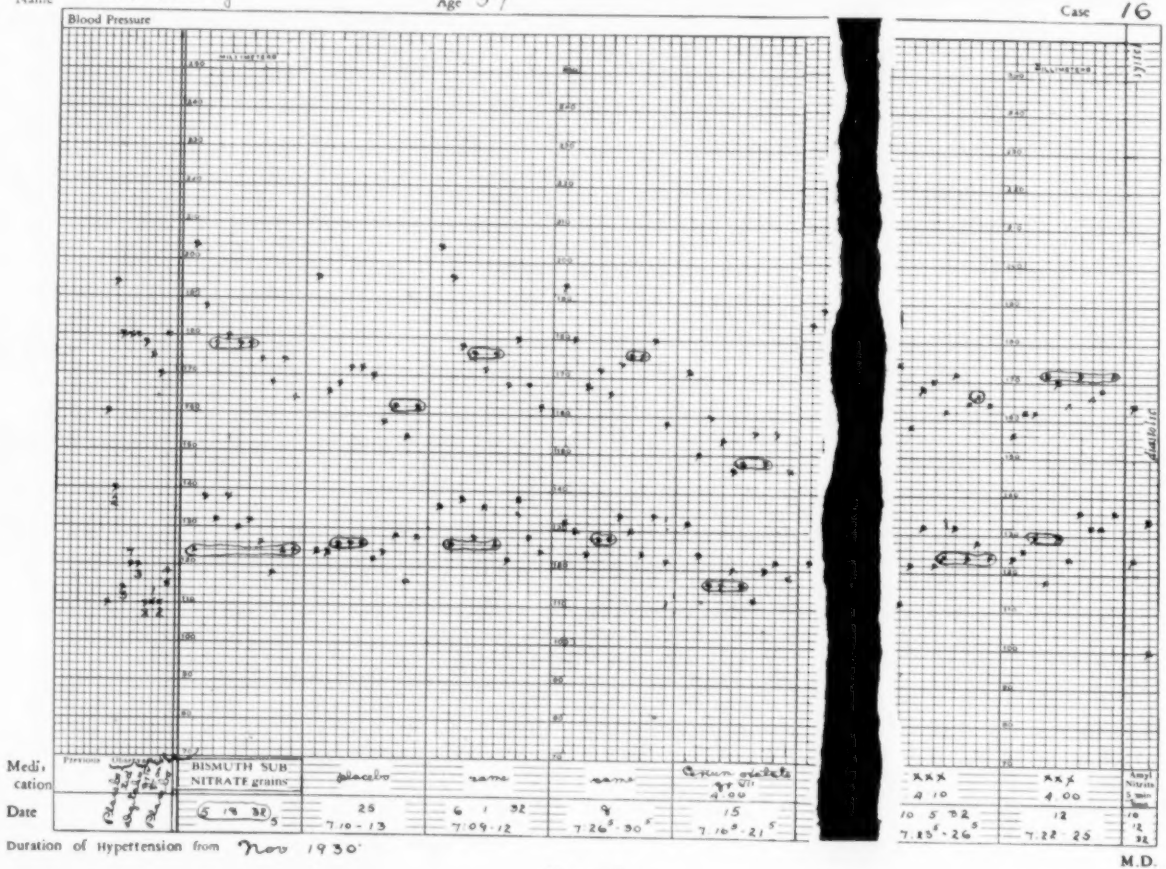
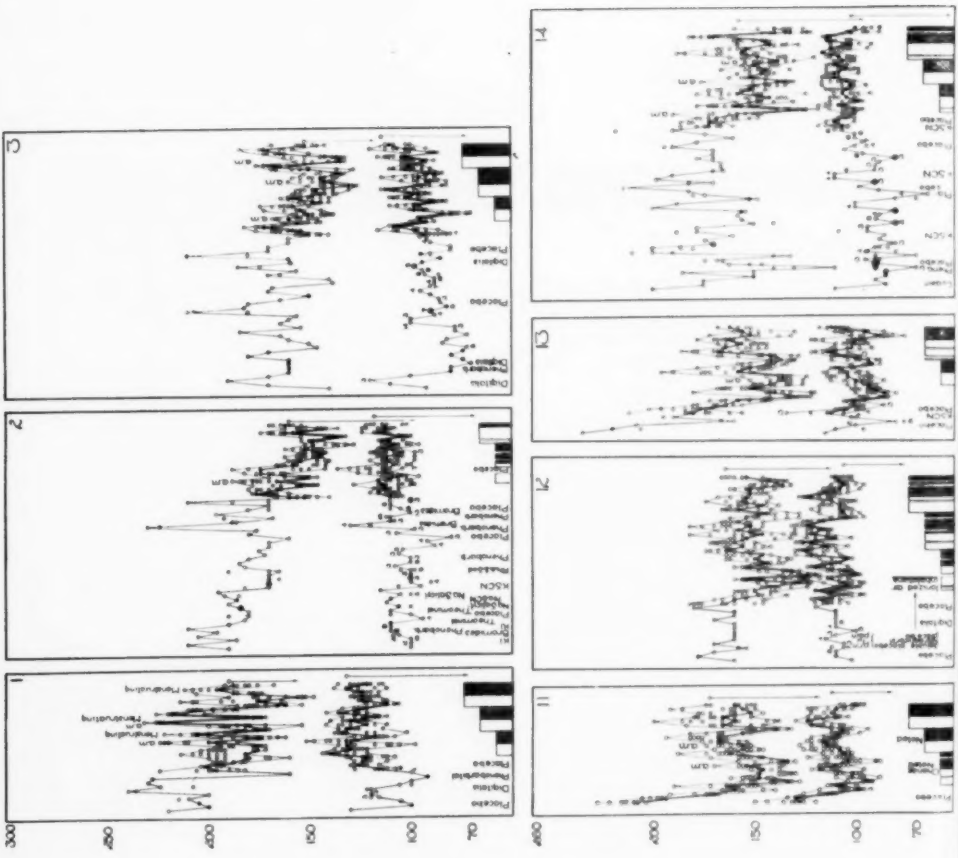

Name Bret, Harry
Age 39
Case 16
Blood Pressure
MILLIMETERS
Medication
BISMUTH SUB NITRATE grains
placebo
same
same
Date
Duration of Hypertension from Nov 1930
M.D.

CHART I.



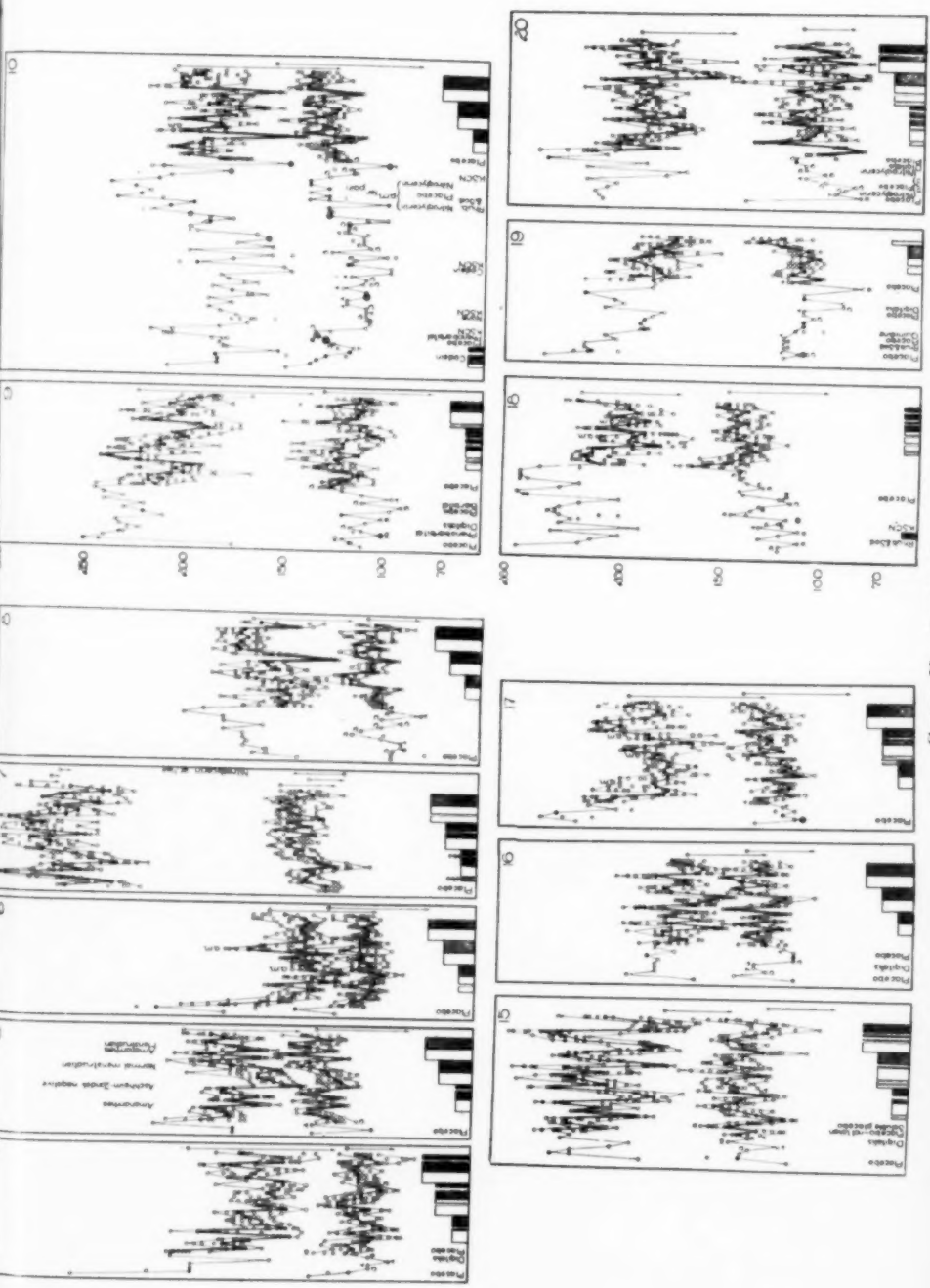


CHART II.—*Continued.*

TABLE 1.—BISMUTH SUBNITRATE BY MOUTH IN ARTERIAL HYPERTENSION.

Cases.	Name: Hospital.	Sex.	Age.	Percentile difference from graded average weight.*	Diagnosis: Etiologic;†	Anatomic;†	Physiologic;†.	Functional.‡	Accompanying condition.	Psychic status.	Stated known duration of hypertension in years.	Years prior observation.	Resistance of peripheral arteries.	Changes in retinal arterioles.	Average control blood-pressure.	Blood pressure after amyl-nitrite.	Blood-pressure variation.	Alteration of symptoms.
1	SG JD	♀	36	+1	Hyp	EH SA	RSR	IIa	Non-toxic goiter	Intensified affective drive	3½	0.5	—	Increased light reflex	181/127	156/72	Continued slight downward trend; wide fluctuation systolic, moderate diastolic	Asymptomatic generally, occasionally transitory symptoms only.
2	AeC JD	♀	59	+3	Hyp	EH	RSR	IIa	...	Neurasthenia; emotional and psychomotor instability	19	3.9	±	Increased reflex, slightly roughened outline	156/112	98/68	Continued slight downward trend; psychogenic rises	Full varied complement of over-elaborated symptoms.
3	AH JD	♀	52	+44	Hyp Art	EH SA	RSR	IIa	History of lues	No abnormality indicated	14	2.7	+	Widened reflex, slight roughening	150/97	118/72	Uniform level; moderate fluctuation	Practically continuous cumulative improvement.
4	RB BI	♀	70	+21	Hyp	EH CS SA	RSR	IIa	...	Depression, self-dramatization, compensatory reactions	2	0.7	+	Increased reflex, slightly nodular outline	157/105	118/88	Cyclic fluctuation	Repeated psychogenic exacerbations.
5	GH BI	♀	27	+49	Hyp	EH	RSR	IIa	...	Emotional instability	6	0.2	—	Slight nodular narrowing	166/125	142/82	Initial upward trend, during which amenorrhea developed; sharp drop after negative Aschheim-Zondek; subsequent decreasing upward trend	Erratic variation in severity and extent.
6	MD JD	♀	57	−25	Hyp	EH	RSR	I	...	Regressive non-adjustive reactions to acute difficulties	1	0.2	—	Increased reflex, nodular narrowing, compression veins	139/105	100/74	Fluctuation within narrow range, occasional isolated elevations	More typical symptoms continuous; psychogenic variable.
7	BA BI	♀	50	+48	Hyp Art	EH SA MI	RSR	IIb	...	Hysterical chorric attacks	½	0	±	Increased reflex, slight narrowing, larger nodular	258/137	276/122 262/118 (256/144)	Slightest downward trend systolic, slight upward diastolic; moderate fluctuation	General improvement, occasional psychogenic attacks.
8	FM BI	♀	57	+36	Hyp Art	EH AI AS	RSR	IIa	...	Slight emotional instability	6	0.9	±	Increased reflex, narrowing, slightly tortuous	153/105	116/82	Slight upward trend systolic, uniform level diastolic, fluctuation	Alternate improvement and exacerbation.
9	RG BI	♀	43	+3	Unk	AI AS MI MS	RSR Hyp	IIa	...	No abnormality indicated	3	1.8	+	Increased reflex, smaller narrowed, compressed bulging veins	208/119	116/82	Moderate irregular fluctuation without trend	Essentially without change.
10	JB	♀	55	+2	Hyp	EH	RSR	IIa	Diabetes	Emotional instab[illegible]								

10	JB JD	♀	55	+2	Hyp	EH	RSR	IIa	Diabetes mellitus	Emotional instability; depression with over-reaction; undefined phobia, largely pathophobia, suppressed during waking by *Mental Science*, rampant during sleep	12	2.7	++	Increased reflex, slightly narrowed, moderately tortuous, indentation veins	187/131	126/84	Slight downward trend systolic, upward diastolic; irregular, slightly cyclic, fluctuation	Asymptomatic, save intermittent paresthesias and neuralgias, probably on basis diabetic neuritis, but apparently with psychogenic incidence.
11	SC JD	♀	48	+10	Hyp	...	RSR	F	...	Slight psychomotor tension	3	0	±	Slightly narrowed and tortuous, slight indentation veins	160/113	118/82	Marked decline during fore-period; subsequent slight upward trend, irregular or cyclic fluctuation	Marked initial improvement, subsequent variation.
12	AaC BI	♀	39	+4	Hyp Art	EH	RSR	IIa	...	No abnormality indicated	1¾	1.1	++	Moderate narrowing, slight tortuosity	150/113	112/76	Irregular fluctuation without trend	Slight cumulative increase.
13	GS JD	♀	50	+15	Hyp	EH	RSR	IIa	...	No abnormality indicated	3	0.4	−	Moderate to extreme narrowing, compression veins	151/100	.....	Early adaptive decline, subsequent cyclic fluctuation	Essentially unchanged.
14	EA JD	♀	73	+27	Hyp Art	EH	RSR MI?	IIa	...	No abnormality indicated	3	2.7	±	Moderate narrowing, slight tortuosity, indentation veins	154/107	96/64	Early slight decline systolic, subsequent narrow fluctuation	General improvement, especially first months.
15	LH BI	♀	47	+24	Hyp	...	RSR	E	...	Emotional instability	2	0.6	+	Narrowing, tortuosity, indentation	202/133	140/88	Wide totally irregular fluctuation without trend	General aggravation, psychogenic increment.
16	HB BI	♂	39	+17	Hyp	EH	RSR	I	...	Neurasthenia: hysterical conversion symptoms	1½	0.6	±	Much narrowing, slight tortuosity, medullated nerve fibers	163/127	124/100	Wide fluctuation without trend, twice higher on bismuth subnitrate	Preponderant improvement.
17	FMcI JD	♀	45	−11	Hyp	EH	RSR	IIa	...	Diffuse persecutory paranoid trend	½	0.5	−	Great narrowing, much tortuosity, indentation veins	183/121	124/82	Initial decline, repeated upward trends terminated by falls	Generally unchanged, psychogenic exacerbations.
18	AM JD	♀	61	+23	Hyp	EH	RSR	I	Diabetes mellitus	No definite abnormality indicated	4	3.7	+	Extreme narrowing; light reflex veins	203/137	170/96	Irregular fluctuation without trend	Paresthesia lower quadrants; diabetic neuritis.
19	IK BI	♀	46	0	Hyp Art	EH	RSR	I	...	No abnormality indicated	1½	1.1	++	.....	182/111	.....	Narrow fluctuation systolic, upward trend diastolic	Initial improvement, subsequent aggravation.
20	RK BI	♀	63	0	Unk	EH AI AS MI MS?	RSR Hyp	IIb	...	Possible incipient senile dementia; querulous over disabilities	4	1.0	+	Very extreme narrowing, perivasculitis, choroidoretinitis	192/106	146/86	Wide irregular fluctuation	Generally unchanged, several brief exacerbations.

* Medico-Actuarial Mortality Investigation, New York, vol. **1**, 1912.

† Abbreviations, initials or first letters of: Hypertension, Arteriosclerosis, Unknown, Enlarged Heart, Sclerosis of Aorta, Coronary Sclerosis, Aortic Insufficiency or Stenosis, Mitral Insufficiency or Stenosis, Regular Sinus Rhythm.

‡ Code letters: I = Able to carry on habitual physical activity. IIa = Slightly diminished physical activity. IIb = Greatly diminished physical activity. E = Possible heart disease. F = Potential heart disease.

retinal arterioles ranged by fine gradations from a minimal increase of the light reflex to extreme narrowing with perivasculitis. The peripheral arteries on palpation were in 5 of normal resistance to compression, in 6 of probably increased resistance not sufficient in degree to be definitely assignable to the vessel wall rather than to its internal pressure, in 6 of definitely increased resistance, and in 3 of markedly increased resistance.

The response to the inhalation of amyl nitrite[5,4,3] was determined in 18 cases (Chart II). Drastic drops in the systolic and diastolic pressures occurred in all but 1 case. This case, which gave only slight and equivocal responses in repeated trials with amyl nitrite and nitroglycerin, registered the highest blood-pressure in the series, showed only an intermediary degree of narrowing of the retinal arterioles, and presented scarcely any definitely increased resistance of the peripheral arterial walls. Neither the absolute nor the relative extent of the response in the remaining cases showed any relationship to the anatomical condition of the radial arteries or the retinal arterioles.

Cardiac hypertrophy occurred in 17 cases. One gave physical signs of aortic valvular lesions, 1 of a mitral lesion, and 2 of combined lesions. Renal involvement of a degree requisite to occasion nocturia was indicated in 18 cases, a tendency to subcriterional specific gravity in 14, traces of albumin in 14, and hyaline casts in 4. An accompanying condition of non-toxic goiter occurred in 1 case, of diabetes mellitus in 2. One gave a history of arrested lues. All had negative blood Wassermann tests.

They, being poor women, were hard beset. No directed effort was made to investigate their psychic status. But in the course of the incidental observation of their behavior on the part of the physician, and the inevitable unburdening on the part of the patients, incident to prolonged clinical observation, sufficient data accrued to assess the psychic status in almost all cases, and to assign diagnoses of minor psychic abnormalities in $\frac{2}{3}$ of the cases. Outright neurasthenia occurred in 2, hysteric manifestations in 3, conditions approaching psychasthenia in 3, and independent or concomitant intensification or instability of affective tone in 7.

Results. The blood-pressure reading nearest the apparent mode of the 10 successive readings was designated as the result of each blood-pressure determination (Chart I). The variation of this modal blood-pressure was regarded as representative of the variation of the blood-pressure during the course of the experiment. The blood-pressure in the several cases pursued a great variety of individual courses (Table 1; Chart II). Its fluctuations were invariably attributable to adventitious factors. In no instance did a drop in the blood-pressure, significant on comparison with the control values, correspond with or accompany the administration of bis-

muth subnitrate. *Throughout bismuth subnitrate was without demonstrable effect on the blood-pressure.* The previous observation of reduction of the blood-pressure in arterial hypertension,[4] made in the absence of the control of immediately preceding non-specific medication, was not confirmed.

The symptoms, dyspnea, palpitation, cardiac pain, dizziness, and headache, described in terms both of their absolute degree and its comparison with that of the preceding visit, because they appeared to be most easily evaluated and most literally reported by the patients, were selected, together with any particularly prominent individual symptoms, as a basis for the generalization of the symptomatic course during the experiment (Table 1). The symptoms also pursued an independent course without reference to the administration or withdrawal of bismuth subnitrate. Bismuth subnitrate was without apparent effect on the symptoms.

Samples of freshly voided urine collected on the last visit of each control period, and on the first and last visits of each experimental period, were immediately tested for nitrite by the addition of sulphanilic acid—α-naphthylamin acetate reagent. With rare exceptions, distributed proportionately between control and experimental periods, the urine tested negative for nitrite. Bismuth subnitrate did not give rise to the excretion of nitrite in the urine.

Summary and Conclusions. 1. Adequate control in the investigation of therapeutic results in arterial hypertension requires provision for both the spontaneous lability of the blood-pressure and the effect of the experimental procedure itself on the blood-pressure.

2. When the experimental procedure is so organized as to provide a standardized method of blood pressure determination, uniform frequency of visits, and the alternation of control periods under non-specific therapy with experimental periods under experimental therapy, any alteration in the blood-pressure which occurs can be either attributed to adventitious factors or interpreted as a therapeutic effect.

3. Such an experimental procedure is self-contained, inasmuch as its control periods are adequate for comparison with its experimental periods, independently of any period of previous observation.

4. Such an experimental procedure, directly applicable to any therapeutic agent that acts without delay, cumulative effects, or retention, and adaptable to therapeutic agents different in these respects, was devised and applied to the investigation of the therapeutic efficacy of bismuth subnitrate.

5. Bismuth subnitrate by mouth, even in the largest therapeutically practicable dosage, does not develop sufficient nitrite action to exert any demonstrable effect on the blood pressure or symptoms of arterial hypertension under the conditions of rigorously controlled experiment.

REFERENCES.

1. Ayman, D.: J. Am. Med. Assn., **95**, 246, 1930; **96**, 2091, 1852, 1931.
2. Stieglitz, E. J.: J. Pharmacol. and Exp. Therap., **32**, 23, 1927; **34**, 407, 1928; Arterial Hypertension, New York: Paul B. Hoeber, Inc., pp. 119, 136, 1930; J. Am. Med. Assn., **95**, 842, 1930; J. Pharmacol. and Exp. Therap., **40**, 343, 1932.
3. Ayman, D.: J. Am. Med. Assn., **98**, 545, 1932.
4. Bruen, C.: J. Lab. and Clin. Med., **18**, 138, 1932.
5. Stieglitz, E. J.: Arch. Int. Med., **46**, 227, 1930.

THE IONTOPHORESIS OF ACETYL-BETA-METHYLCHOLIN CHLORID IN THE TREATMENT OF CHRONIC ARTHRITIS AND PERIPHERAL VASCULAR DISEASE.*

PRELIMINARY REPORT.

BY JOSEPH KOVACS, M.D.,

ASSISTANT IN MEDICINE, NEW YORK POST-GRADUATE MEDICAL SCHOOL OF COLUMBIA UNIVERSITY; ASSISTANT PHYSICIAN, DISPENSARY, NEW YORK POST-GRADUATE HOSPITAL, NEW YORK, N. Y.

(From the Arthritis and Vascular Clinics of the Department of Medicine of the New York Post-Graduate Medical School and Hospital of Columbia University.)

THE discovery that cholin compounds relieve vascular spasm and increase peripheral circulation induced me to experiment with them in chronic arthritis, where we deal generally with disturbed circulation, and in the spastic types of peripheral vascular disease.

The importance of circulatory disturbances in chronic arthritis is generally recognized and it is believed by many to be an essential factor in causing and maintaining a rheumatic condition. The poor circulation may be considered as an etiologic factor in this symptom complex, although definite proof in this regard is still lacking.

It was found by Wright and Pemberton,[1] Rhumann,[2] Lunedei and Corradini,[3] and ourselves[4] that disturbances of the circulation frequently accompany and undoubtedly aggravate chronic arthritis, hence the improvement of disturbed circulation plays a prominent rôle in the therapy of arthritis.

The usefulness of the acetyl-cholin group to increase peripheral circulation has been limited by the fact that it is rapidly destroyed by body fluids and blood. Recently another compound of cholin—acetyl-beta-methylcholin chlorid†—has been studied by Simonart.[5] His investigation seems to indicate that acetyl-beta-methylcholin chlorid offers greater possibilities of clinical usefulness. He claims that it is destroyed more slowly in blood and body fluids, is more potent, and lacks almost entirely certain undesirable by-effects of acetyl-cholin. On normal persons and in peripheral vascular diseases, when administered subcutaneously, its action begins within 2 min. and ceases within 15 to 20 min. (Starr and collaborators).[6]

* Aided by grants from the Josiah Macy, Jr., Foundation.

† Synthetized by R. T. Major and J. K. Cline, J. Am. Chem. Soc., **54**, 242, 1932.

There is a slight fall of blood pressure, rise of pulse rate, flushing, sweating, and increased salivation. Administered by mouth its action begins within 15 to 75 min., lasts ½ hour to 1 hour, and is much milder.

When drugs are administered in a diluted solution and given subcutaneously or intravenously, or taken by mouth, the effective ions are absorbed by the blood and distributed to all parts of the body, even though they are more needed locally. In the case of cholin compounds the local effect is greatly reduced because much of the drug is destroyed by the blood. In order to obtain a more effective local result the induction of acetyl-beta-methylcholin chlorid by iontophoresis (medical ionization) was attempted in the experiments herein reported.

In this method the ions are introduced locally from the surface, and there is only a slight general effect due to the absorption into the blood stream. Iontophoresis is accomplished by the use of galvanic current: if pad electrodes are soaked in a diluted solution of drugs and connected to a source of galvanic current, the ions of these drugs penetrate into the tissues under the effect of the suitable pole. The factors of the depth of penetration theoretically depend (1) on length of time the current flows, (2) on the electromotive force, (3) on the weight of the ions, and (4) on the tissues being treated.

Technique. A 1% solution of acetyl-beta-methylcholin chlorid (1 gm. in 100 cc. of water) is employed. The drug being an alkaloid with a positive charge, can be introduced into the tissues from the positive pole only. Reinforced asbestos fabric paper is saturated with the solution and wrapped around the affected joints. A fairly large malleable metal plate is placed over the wet asbestos paper and connected to the positive pole of a galvanic generator. A dispersive, very large, regular moist pad electrode is applied to the back or abdomen and is connected with the negative pole.

The current is turned on and slowly increased to 20 to 30 milliamperes, always being kept within comfortable toleration to the patient. Treatments of 20 to 30 min. are employed. To avoid the possibility of burns, care must be taken that the metal electrode or electrode clamps do not come in direct contact with the skin. The asbestos paper is more satisfactory than gauze or blotting paper for it absorbs less fluid and keeps moist for a longer time. We often treat two regions of the body at the same time, with the help of a bifurcated cable from the positive pole. After treatment, the part treated is dried and kept covered.

Physiologic Effects. *Local.* 1. "Gooseflesh," due to the contraction of the erector muscles of the hair follicles, was observed immediately after treatment and disappears within 10 to 30 min.

2. Sweating was observed immediately after treatment and continues for 8 to 10 hours. It is probably due to a direct action of the drug on the sweat glands, or their nerve supply.

3. Increase of skin temperature in cases where a spasm of the peripheral blood supply was present. The increase of temperature varied between 4 to 10° F. and remained for 2 to 4 hours.

4. Increase of rate of capillary flow without enlargement of the capillaries. The number of visible capillaries were not increased after treatment.

5. Slight redness of the skin which remained for 1.5 to 2 hours, due probably to the enlargement of the deeper small arteriole vessels.

6. Increased salivation when treatment was applied in the region of the salivary glands.

7. A questionable slight increase in the local leukocyte count was noted. Differential and total blood counts taken before and immediately after treatment from the treated part showed no change in the differential count, but a slight increase in the number of leukocytes (600 to 1000—in 1 case 3000). This was a constant finding but is recognized to be within the limits of error.

8. Warm feeling of the treated part for 24 to 72 hours; after repeated treatments, for longer periods; in some cases for a whole week.

9. In certain patients increased oscillometric readings were noted.

10. Reduction of swelling and increased mobility.

11. Relief of pain.

General Effect. When large areas were treated we often also observed a general effect causing flushing, sweating, increase of pulse rate and salivation, slight lowering of blood pressure and evidence of intestinal peristalsis. The intensity of these symptoms varied individually. They started generally after 1 to 10 min. and ceased right after the treatment was brought to an end.

Therapeutic Results. While this series of patients is too small and followed for too short a time to draw definite conclusions concerning the permanent value of the treatment, the results warrant presentation of evidence as a guide to future work.

Chronic Arthritis. Forty chronic rheumatic patients have been treated: 16 rheumatoid arthritics, 14 osteoarthritics, 3 cases of bursitis, 3 of sciatica, and 4 of neuritis.

In order to evaluate the obtained results, it was necessary to establish a principle on which to base conclusions. We regarded it as an improvement only if there was a definite reduction in pain, swelling and stiffness, with increase of function and lessening of deformities. Patients had for the first 3 to 4 weeks 2 treatments weekly, later 1. Most of the selected cases were old clinical patients who had previously had, in addition to general treatment, all other kinds of local treatment, such as diathermy, short-wave fever treatment, Roentgen ray treatment, etc., without relief of pains or improvement of symptoms. We did not change the form of general treatment, as we wished to gain a clear picture of the reaction of the iontophoresis.

The most promising results were obtained in the otherwise stubborn cases of rheumatoid arthritis; 95% of the cases showed improvement. These good results were anticipated in rheumatoid arthritis because this is the type of arthritis in which we have found the most pronounced circulatory disturbances. Two cases, after 2 months

of treatment, were symptom-free and have been without any complaint for the last 3 months, but most of the cases are still under treatment with improved condition.

In the osteoarthritic type the results were likewise encouraging. In this type of arthritis other therapeutic measures like heat, diathermy, massage, etc., had given satisfaction. With acetyl-beta-methylcholin chlorid iontophoresis there was a definite improvement in 80% of the cases.

There was full recovery in the 3 cases of sciatica, where diathermy and galvanic treatment had failed to give relief. All the sciatica cases were in a toxic or infectious stage without any changes in the bone structure of the spine.

In the 3 cases of bursitis 2 responded quickly but in the 3d case the treatment failed to give relief.

The 4 neuritis cases reacted well to the treatment and in every case there was a quick full recovery.

In both types of arthritis where the patients had definite swellings we observed after treatments a reduction of the swelling and an increased capillary circulation. Further studies are necessary to determine whether the increased capillary circulation is responsible for the reduction of swelling or whether the reduction of swelling relieving the tension of the tissues facilitates the capillary circulation.

This is not an attempt to create the impression that acetyl-beta-methylcholin chlorid iontophoresis is a specific therapy for chronic arthritis. Chronic arthritis must be considered as a systematic disease, with local manifestations in the joints. Treatment of the disease must be done primarily through systemic general measures, to which local measures are added. These local measures are equally important because they relieve painful and uncomfortable local symptoms of the patient and tend to prevent or ameliorate local organic changes. Acetyl-beta-methylcholin chlorid iontophoresis is a local therapeutic measure and thus far seems to promise more satisfactory results than other local therapeutic measures.

Peripheral Vascular Disease. It was felt that because of the physiologic effect and the clinical results of this treatment it might be of value in the treatment of the group of peripheral vascular diseases in which spasm is the chief factor.[7] In the few cases treated desirable results have been obtained, namely, release of spasm with increased circulation. As noted by surface temperature, elevation and improvement of the capillary circulation; other symptoms also showed improvement. Chronic vascular ulcers have shown unusually rapid healing powers. This series is being further enlarged and studied and will be the subject of a later report.

In spite of the pronounced local action and good therapeutic results, we must admit that we still do not know precisely how much of the drug is absorbed by the tissues with the iontophoresis method and how deep the drug penetrates. Further investigation is needed

to explain the exact action of acetyl-beta-methylcholin chlorid iontophoresis on the local circulation and sweat glands.

That the effect of acetyl-beta-methylcholin chlorid iontophoresis is specific and not a simple galvanic effect was demonstrated in the following way: both hands of a patient were treated at the same time—one hand with the drug and the other with normal salt solution. Both hands were connected to the positive pole with the help of a bifurcated cable. The indifferent negative electrode was at the back. After 20 min. treatment with a 20 milliamperes strong galvanic current, the hand with normal salt solution remained cold. There was no sweating, only a slight redness in patches and the capillary picture remained unchanged. The hand treated with the drug showed all the characteristic symptoms of acetyl-beta-methylcholin chlorid iontophoresis; as increased skin temperature, sweating (which continued 6 to 10 hours), gooseflesh, faster capillary flow and a slight diffuse redness.

The effect of acetyl-beta-methylcholin by iontophoresis is not confined to a skin area, and hence is quite different from a simple counter irritant. The general reaction points to the absorption of the drug into the general circulation. The therapeutic effect of this form of treatment might be explained by the deposition of the drug in the superficial tissues and its slow absorption from there, giving prolonged slight general vasodilatation, combined with a pronounced and prolonged local effect.

Conclusions. 1. A preliminary report on the action of the iontophoresis of acetyl-beta-methylcholin chlorid is presented.

2. Acetyl-beta-methylcholin chlorid introduced locally with the help of the galvanic current produces a pronounced and prolonged local effect which cannot be obtained through subcutaneous or oral administration.

3. This local treatment appears to be of value in chronic arthritis, especially in the rheumatoid type.

4. This treatment may also be of value for patients with peripheral vascular disease in which spasm is an important factor.

5. No harmful general effects were observed.

6. Further studies with prolonged observation of cases, especially in view of the fallacies lurking in the evaluation of the therapeutic test, are essential for the correct evaluation of this method.

REFERENCES.

1. Wright, L. M., and Pemberton, R.: Arch. Int. Med., **45**, 147, 1930.
2. Ruhmann, W.: Acta Rheumatol., **2**, 29, 1930.
3. Lunedei, A., and Corradini, G.: Ibid., p. 2.
4. Kovacs, J., Wright, I., and Duryee, A. W.: J. Am. Med. Assn., **100**, 1018, 1933.
5. Simonart, A.: J. Pharm. and Exp. Therap., **46**, 157, 1932.
6. Starr, I., Elsom, K. A., Reisinger, J. A., and Richards, A. N.: Am. J. Med. Sci., **186**, 313, 1933.
7. Wright, I. S.: J. Am. Med. Assn., **101**, 439, 1933.

THE BONE MARROW IN IDIOPATHIC THROMBOPENIC PURPURA.

By John S. Lawrence,
ASSOCIATE PROFESSOR OF MEDICINE,
AND
Ralph E. Knutti,
INSTRUCTOR IN PATHOLOGY, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, NEW YORK.

(From the Departments of Medicine and Pathology, University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and the Rochester Municipal Hospitals.)

Remarkably few studies of the bone marrow in idiopathic thrombopenic purpura have been reported.[3,4,7,11,12] All of these reports, except that of Minot,[7] have presented evidence of abnormalities of the megakaryocytes and thus have given substantial support to the theory of Frank[2] as to the pathogenesis of this condition. Notwithstanding this fact, the prevailing opinion in American textbooks of medicine is that there are no changes of note as regards the megakaryocytes in the bone marrow in this disease. Minot and Buckman[1] make a statement to the effect that the few human cases studied postmortem "show no decrease in the number of megakaryocytes, which suggests that defective formation of platelets does not necessarily occur in this idiopathic form of the disease." Sturgis[8] states that "the bone marrow does not show characteristic changes; there does not appear to be a reduction in the number of megakaryocytes." No statement as to the bone marrow in this condition is made in Osler and McCrae's Principles and Practice of Medicine.[10] On the other hand, Naegeli[9] holds that a bone marrow disorder lies in the forefront in this condition.

In view of the fact that the studies which have been made on the bone marrow of patients with this disorder have been few and have not led to uniform results, we have been studying during the past 3 years morphologic characteristics of the bone marrow of a small series of patients with this type of purpura. The sternal marrow has been studied in most of our patients, as this was found to be the easiest to obtain from living subjects. The marrow from other locations was studied postmortem in a few cases. The marrow has been found to be essentially normal in 4 of 6 patients with the typical findings of idiopathic thrombopenic purpura. In the other 2 patients the megakaryocytes were diminished in numbers and appeared abnormal.

Methods and Results. We have relied mainly upon the findings in sections of marrow stained with hematoxylin and eosin. Other stains—Giemsa, Jenner-Giemsa, Wright's and supravital neutral red, have been used also in part of the cases. We regret that complete studies of this nature were not made in all of our patients. Such stains are now included in the routine study of all of the specimens of marrow removed from the sternum in this clinic.

Case Reports. Case 1.—M. W. (Unit No. 31010). Married woman, aged 31, presented the typical history and clinical findings of chronic idiopathic thrombopenic purpura—repeated epistaxis, purpuric lesions in skin, profuse menstrual bleeding. The red blood cell count was 4,580,000 per cmm. The hemoglobin was 75% (Sahli). The white blood cell count was 7350 per cmm. and the differential count was normal. The blood platelets were markedly reduced, a fixed stained smear showing about 1 normal platelet per oil-immersion field. The bleeding time was 6 min. The coagulation time (test-tube method) was 15 to 18 min. The clot was very friable and broke upon an attempt being made to pick it up.

A specimen of marrow was removed from the sternum. A section of this stained with hematoxylin and eosin showed no apparent decrease in the number of the megakaryocytes and no morphologic abnormalities of these cells. The eosinophilic myelocytes were not increased. The other marrow cells were present in proportionately normal numbers. Smears stained with Giemsa and Jenner-Giemsa stains revealed an entirely normal picture.

Impression. Normal bone marrow. Chronic idiopathic thrombopenic purpura.

Case 2.—E. P. (Unit No. 52088). Married woman, aged 36, had a classical history for chronic idiopathic thrombopenic purpura. The laboratory findings were typical of this condition, the only unusual finding being a persistent leukopenia. The number of leukocytes varied between 1620 and 6600 per cmm. (average of 46 determinations, 3633). Repeated differential counts revealed normal percentages of the various white blood cells. The number of the red blood cells varied between 3,140,000 and 5,180,000 and the percentage of hemoglobin between 60 and 103 (Sahli). The percentage of reticulocytes remained low, the highest figure being 6 and the lowest 1.2. The bleeding time was prolonged, 6, 8, 12½, 23, 27½ and 30½ min. The coagulation time was 8 to 14 min. (test-tube method). The clot was friable and did not retract.

Bone marrow, removed from the sternum on December 10, 1931, and stained with hemotoxylin and eosin, showed abundant marrow cells. There was no appreciable reduction in the number of the megakaryocytes and morphologically, these cells appeared to be normal. The eosinophilic myelocytes were numerous and seemed to be slightly increased in numbers. The other cells appeared to be normal.

Impression. Normal bone marrow. Chronic idiopathic thrombopenic purpura.

Case 3.—S. B. (Unit No. 26047). Married woman, aged 23, whose illness was characterized by evidence of a hemorrhagic diathesis—bleeding from gums, nose and vagina. The duration of the illness was 3 months. She was under observation in the Rochester Municipal Hospital during the last 3 weeks of life. The red blood cell count remained between 1,610,000 and 2,400,000 per cmm. The hemoglobin varied between 24 and 40% (Sahli). The number of the white blood cells fluctuated between 16,050 and 12,300 per cmm. The differential counts were normal. The percentage of reticulocytes was 10 on one occasion and 5.7 on another. The platelets were markedly reduced, none being found in a fixed stained preparation on two occasions and only a very few on another. The coagulation time (test-tube method) was 8 to 12 min. There was no clot retraction. The clot was rubbery and elastic. The bleeding time was greater than 30 min. Blood was found in both urine and stool specimens. The patient died 23 days after admission to the hospital.

Autopsy. The bone marrow from the midfemur was uniformly dark red. All fat seemed to have been replaced. A section stained with hematoxylin and eosin revealed evidence of a moderately hyperplastic marrow. The megakaryocytes were quite numerous. They varied in size, many of

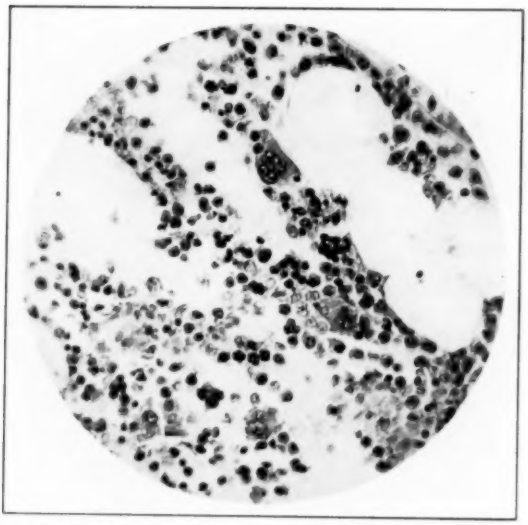


FIG. 1.—A typical field from a section of marrow from the femur of Case 4. Hematoxylin and eosin stain. (× 430.) Note the presence of megakaryocytes with large vesicular nuclei.

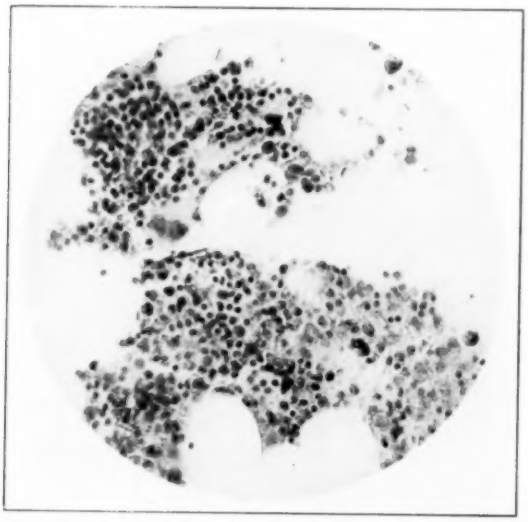


FIG. 2.—A typical field from a section of the sternal bone marrow of Case 5. Hematoxylin and eosin stain. (× 430.) Three megakaryocytes are present; 2 of these have heavy staining close-textured nuclei.

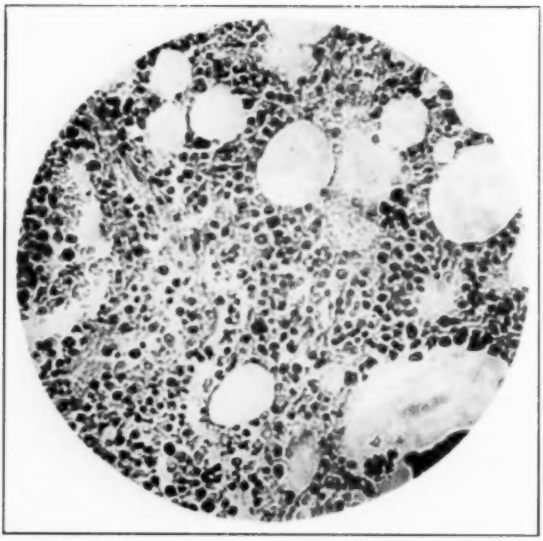


FIG. 3.—A typical field from a section of the sternal bone marrow of Case 6. Hematoxylin and eosin stain. (× 250.) No megakaryocytes are present.

them being only about ½ as large as usual. Most of these smaller cells had shrunken, dark-staining irregular nuclei with a small amount of pink cytoplasm. Most of the larger megakaryocytes had small, round, clear nuclei with abundant pale cytoplasm. A few of them showed shrunken, dark-staining nuclei with more deeply pink cytoplasm. Eosinophilic myelocytes were not relatively increased in numbers. The other marrow cells, though abundant, showed no distinct changes.

Impression. Hyperplastic bone marrow with morphologic variations of the megakaryocytes. Acute idiopathic thrombopenic purpura.

CASE 4.—S. M. (Unite No. 24234). Widow, aged 48, gave a history of generalized purpura for 5 weeks and tarry stools for a few weeks. On the morning of admission she suddenly developed twitching of the left forearm and hand and then became paralyzed. She became comatose and died the day after admission. Her red blood cell count was 3,000,000 per cmm. The hemoglobin was 65% (Sahli). The white blood cell count was 7500 per cmm. and the differential count was normal. No platelets were found in a fixed smear stained with Wright's stain. The capillary clotting time was 5 to 6 min. The clot did not retract. The urine gave a strongly positive guaiac test.

Autopsy. The bone marrow from the middle of the right femur was grayish-red and seemed to have retained only a small amount of the usual fat. The marrow of the lumbar vertebræ was pale grayish-red. That of the ribs was diminished in amount and had a pinkish-gray color. Sections from the ribs, vertebræ and femur (Fig. 1) were stained with hematoxylin and eosin. The marrow was of normal amount. Frequent megakaryocytes were present. Most of these were large cells with a uniformly pink cytoplasm and with numerous round to oval clear finely stippled nuclei. Very few were noted with deep blue nuclei. Eosinophilic myelocytes seemed slightly increased in numbers. The other cells showed no abnormalities.

Impression. Slightly hyperplastic bone marrow. Acute idiopathic thrombopenic purpura.

CASE 5.—R. T. (Unit No. 47855). Unmarried male, aged 19, gave a history of recurrent severe epistaxis for 2 years. For 10 days he had had generalized purpuric areas. His red blood cell counts varied between 4,660,000 and 5,100,000 per cmm. with hemoglobin values between 80 and 90% (Sahli). The white blood cell counts fluctuated between 3500 and 7200 per cmm. The differential counts were normal, the neutrophils representing 57 to 76% of the cells. The percentage of reticulocytes was 3. In fixed stained smears, the platelets were absent or very rare. The bleeding time was greater than 1 hr. The coagulation time (test-tube method) was 12 min. The clot was soft and jelly-like.

A specimen of sternal bone marrow was removed on March 21, 1932. A section of this stained with hematoxylin and eosin was not entirely satisfactory, due to the small amount of marrow. However, the number of megakaryocytes appeared less than normal and a good percentage of those present had heavy-staining nuclei of the close-textured type. Supravital neutral red, Giemsa and Jenner-Giemsa preparations showed less megakaryocytes than normal. The other marrow cells appeared normal (Fig. 2).

Impression. Reduced number of megakaryocytes in the bone marrow. Chronic idiopathic thrombopenic purpura.

CASE 6.—R. K. (Unit No. 75955). Unmarried man, aged 41, had had ecchymoses and numerous petechiæ on frequent occasions for 15 years. On one occasion he had had slight bleeding from the gum. Epistaxis had occurred only occasionally. His red blood cell count was 2,970,000 per cmm. The hemoglobin was 10.5 gm. per 100 cc. The reticulocytes were 0.1%. The volume of packed red blood cells was 35.4 cc. The mean corpuscular volume was 119.2 cc. The mean corpuscular hemoglobin was

35.3$\gamma\gamma$. The mean corpuscular hemoglobin concentration was 29.6%. The white blood cell count was 4200 and the differential count was normal. There was about 1 platelet to each 6 to 8 oil-immersion fields in a fixed smear stained with Wright's stain. The bleeding time was 5 to 8 min. The coagulation time (test-tube method) was 8 min. The clot retracted poorly.

A specimen of marrow was removed from the sternum (Fig. 3). Sections of this stained with hematoxylin and eosin revealed a relatively abundant cellular content. The eosinophilic myelocytes appeared to be increased in numbers. The number of the megakaryocytes was markedly diminished, only 3 or 4 being found in each section. Only one of these appeared normal. The others showed a very scanty cytoplasm. Their nuclei were dark blue, shrunken and finely granular. The other marrow cells appeared normal.

Impression. Reduced numbers of megakaryocytes in the bone marrow. Chromic idiopathic thrombopenic purpura.

Discussion. Our observations are not wholly in accord with either of the two more important theories (Frank[2], Kaznelson[5]) as to the mechanism responsible for the diminished number of platelets in the peripheral blood of patients with idiopathic thrombopenic purpura. The failure to find any abnormal changes of note in the bone marrow of 4 of the patients supports the contention of Kaznelson that the primary disorder is not in the bone marrow. The fact that the morphologic appearance of the bone marrow presented no marked changes does not prove, however, that the marrow was functionally normal. Nevertheless, from these findings it would be impossible to say that the platelets were not destroyed after entering the peripheral circulation and that the spleen was not probably the most important center for this destructive process.

The presence of diminished numbers of megakaryocytes in 2 of the cases presenting the typical picture of idiopathic thrombopenic purpura supports Frank's original idea that the primary disorder lies in the bone marrow. The cases reported by Seeliger,[12] Jedlicka and Altschuller,[4] Schmincke[11] and Gerlach[3] further support this theory. Finally the findings in 1 of our patients (not included in this report) who had an aplastic marrow at death but who several months previously had had marrow which was capable of regeneration is in conformity with Frank's theory. Our impression is that this patient had marked aplasia of the megakaryocytes and slight aplasia of the granulocytes when first observed. Later the red cell function of the marrow was involved also and aplastic anemia resulted.

In view of the fact that our observations have shown clear-cut evidence of bone-marrow involvement in some patients with idiopathic thrombopenic purpura and in others no involvement of the marrow, we are inclined to think that there are at least two different types of this condition insofar as the bone marrow is concerned. Lescher and Hubble[6] have previously made a suggestion of this same nature. We have felt that those cases of chronic idiopathic thrombopenic purpura which presented normal morphologic bone-marrow findings would be more likely to profit by splenectomy than would those who had an abnormal bone marrow. Our series of

cases is much too small to justify any positive assertion in this connection. It would seem to us advisable to have sternal bone-marrow studies on all such patients prior to operation. If such observations are recorded in various clinics, it may be possible to determine whether the prognosis as regards the effect of splenectomy can be more correctly evaluated by knowing the bone-marrow picture.

It may be stated here that we have never encountered any trouble from removing marrow from the sternum of patients with diminished numbers of platelets and abnormal coagulating mechanisms. In addition to the cases here reported, we have removed bone marrow from the sternum of several additional individuals, some of whom had symptomatic thrombopenic purpura. We have always either given the patients a transfusion before operation or else have had a donor available in case of bleeding after operation. As a routine measure, we would suggest that the sternal marrow be removed within 48 hours after transfusion and that a donor be on hand in case postoperative bleeding should occur.

Conclusions. 1. The bone marrow in idiopathic thrombopenic purpura may present no abnormal morphologic characteristics or it may show changes as regards the megakaryocytes.

2. It is suggested that there may be two types of this disease on the basis of the bone-marrow picture.

3. The question has been raised as to the probable value of bone-marrow studies in regard to determining the prognosis from splenectomy in patients with chronic idiopathic thrombopenic purpura.

BIBLIOGRAPHY.

1. Cecil, R. L.: A Text-book of Medicine, Philadelphia, W. B. Saunders Company, 1931.
2. Frank, E.: Berl. klin. Wchnschr., **52**, 490, 1915.
3. Gerlach, G.: Centralb. f. Allg. Path., **48**, 81, 1930.
4. Jedlicka, V., and Altschuller, G.: Acta med. Scand., **64**, 123, 1926.
5. Kaznelson, P.: Wien. klin. Wchnschr., **29**, 1451, 1916.
6. Lescher, F. G., and Hubble, D.: Quart. J. Med., **1**, 425, 1932.
7. Minot, G. R.: Arch. Int. Med., **19**, 1062, 1917.
8. Musser, J. H.: Internal Medicine, Philadelphia, Lea & Febiger, 1932.
9. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, 5th ed., Berlin, Julius Springer, 1931.
10. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, New York, D. Appleton and Company, 1930.
11. Schmincke (Heidelberg): Verhandl. deutsch. path. Ges., **25**, 50, 1930.
12. Seelinger, S.: Klin. Wchnschr., **3**, 731, 1924.

MEGAKARYOCYTOSIS IN WHITE MICE WITH SPONTANEOUS MAMMARY CARCINOMAS.

By W. C. Hueper,
PHILADELPHIA, PA.

The origin and histogenesis of extramedullary megakaryocytes in the organs of the human adult have been for some time the subject of a lively discussion (Petri,[1] Downey, Palmer and Powell[2]).

Some investigators (Aschoff,[3] Lubarsch,[4] Goroncy[5] and others) claim that the heterotopic occurrence of these cells in the lung, liver, spleen, kidney and lymph nodes is always of an embolic nature caused either by a mechanical trauma to the bone marrow (fracture) or resulting from a hyperactivity of this tissue, in the course of which megakaryocytes are swept out into the circulation (septicemia, pneumonia) (MacCallum[6]) (polycythemia, leukemia). Other workers, however, maintain that extramedullary megakaryocytes are, at least in part, of autochthonous origin, especially in conditions accompanied by heterotopic hematopoietic foci (leukemia, pernicious anemia, etc.) (Koerner,[7] Naegeli,[8] Barth,[9] Morawitz and Denecke,[10] and others); that is, in diseases which are characterized by the reappearance of myeloid cellular elements in organs, from which they normally disappear toward the end of fetal life (Schridde[11]). This conception is supported by the experimental results of Kuczinski[12] and Custer,[13] who used mice and rabbits respectively in their work.

During certain investigations upon white mice with spontaneous mammary cancers, a high incidence of extramedullary megakaryocytes in various organs was noted, thereby substantiating the observations previously made by Hill[14] and Waterman.[15] Considering, moreover, the fact that cancer-bearing mice rather often show extramedullary lymphoid and myeloid foci in various organs, which sometimes reach leukemoid proportions (Jaffé,[16] Hill,[14] Simonds,[17] and others) and are, therefore, comparable to those pathologic conditions of the human hematopoietic system, which are not infrequently associated with heterotopic megakaryocytosis, the carcinomatous mouse appears to be a suitable source for collecting additional information on the origin and histogenesis of heterotopic megakaryocytes.

The present communication is based upon the histologic examination of the organs of 210 white mice, 172 of which had spontaneous mammary carcinoma, while 38 were normal white mice of the same strain. Of the cancer mice 91 and of the normal animals 19 had been subjected to Roentgen ray treatments of varying intensity, the total doses, ranging from 40 *r* to 6000 *r* in the different animals, delivered over a period of from 1 to 6 weeks. Twenty-one cancer animals were untreated and had died a natural death, while the remaining animals had received at some time during their lifetime injections of various kinds of organic and inorganic chemotherapeutic substances.

In view of the fact that megakaryocytes and small accumulations of myelocytes are often present in moderate number in the spleen of normal mice and considering that, as has been mentioned before, these elements are usually found in increased numbers in the spleens of carcinomatous mice, the description of the effects of the various treatments given may be restricted to those types of treatment

which produced changes in these normal conditions. It was noted that in a series of 31 cancer animals and 19 normal mice the application of Roentgen rays (1000 *r* to 6000 *r*) caused a more or less complete disappearance of the hematopoietic tissue in the organs of the majority of these animals. The application of smaller doses especially of very small ones (30 *r* to 90 *r*), over a prolonged period and at longer intervals, seemed to have resulted in an increase in the amount and incidence of myeloid tissue in various organs, confirming the observations of Fischer-Wasels and Buengeler[18] and others.

The series treated with the various chemical agents did not show any appreciable differences from the conditions seen in untreated animals.

A histologic examination was made of the following organs: Tumor, lung, heart, liver, pancreas, spleen, lymph nodes, kidney, suprarenal gland and brain. All sections were carefully studied for the presence of megakaryocytes. A longitudinal section was made through the spleen, or in cases with markedly enlarged spleens, the section was prepared from $\frac{1}{2}$ of the spleen. Splenic enlargements were rather frequent in the carcinomatous mice and sometimes reached huge proportions. The relative frequency of megakaryocytes in the spleen was determined from the histologic study of the sections and was recorded in the following manner: none, 0; scanty, +; moderate, ++; many, +++; very numerous, ++++. A similar type of evaluation of splenic megakaryocytes was recently used by Waterman.[15]

If the 172 spleens of the carcinomatous series are grouped according to the frequency of megakaryocytes, the following compilation is obtained:

	0	+	++	+++	++++
Cancer series	18 (11)*	11 (5)	61 (9)	58 (5)	23 (1)
Tar cancer series of Waterman	3	8	9	9	5
Normal series	11	6	8	10	3
Tar refractory series of Waterman	9	8	8	2	2

* The numbers in parentheses designate animals which had been exposed to heavy irradiation with Roentgen rays. The destructive effect of the rays upon the megakaryocytes is obvious.

These figures illustrate well the high incidence of megakaryocytes in the spleen of mice with spontaneous carcinoma and compare well with those obtained by Waterman[15] in mice with tar cancers and in mice refractory to tar.

The increase in the number of splenic megakaryocytes in the cancer mice is to a certain extent reflected in the incidence of these cells in other organs. In 36 mice megakaryocytes were found in extrasplenic locations: 25 times in the liver alone, in 6 instances in the liver and lung and once in liver and kidney, twice in the lung and twice in lymph nodes.

Heterotopic megakaryocytes were found in:

	Times.
Liver	32
Lung	8
Lymph node	2
Kidney	1

A certain parallelism exists between the occurrence of extrasplenic megakaryocytes and the number of these cells in the spleen.

	Frequency in the spleen.				
	0	+	++	+++	++++
Extrasplenic megakaryocytes in:					
Cancer mice	0	1	11	12	4
Normal mice	0	1	0	1	2

The extrasplenic megakaryocytes in the normal series were found in 3 instances in the liver and once in a lymph node.

The compilations given above show quite definitely that heterotopic megakaryocytes in white mice are most numerous in the spleen and liver and are far less so in the lung and kidney. This observation concerning the relative frequency and distribution of heterotopic megakaryocytes in mice agrees well with that made by Koerner[7] in a case of myeloblastic leukemia, where the largest number of megakaryocytes was observed in the spleen, liver and lymph nodes, while they were much less numerous in the lung and kidney.

Goroncy,[5] however, found in his series of 27 cases of extramedullary megakaryocytosis quite different numerical relations. Megakaryocytes were present in the lung 17 times, liver 14 times, spleen 9 times. He noted, moreover, that these cells were most numerous in the lung.

The marked contrast between the observations of Goroncy[5] and those made by us in mice suggest that heterotopic megakaryocytes found in mice do not all represent cell emboli of medullary origin, but are at least in part of local genesis. This conception receives additional support from other observations (Kuczinski; Custer; Downey, Palmer, and Powell and others).

Though Goroncy found that many of the extramedullary megakaryocytes consisted only of bare nuclei, the cytoplasm supposedly being stripped off during their passage through narrow vessels, the megakaryocytes seen in the spleen, liver and lymph nodes of mice were usually well preserved and without any signs of mechanical cellular destruction, indicating that these cells had not been exposed to such trauma (Siegmund[23]).

It was furthermore noted that the megakaryocytes in the spleen were not infrequently grouped in smaller and larger clusters, similar to those seen in the bone marrow as the result of regenerative megakaryocytic proliferation. Considering the fact that these megakaryocytic accumulations consisted of young and old cells, their embolic nature appears to be unlikely.

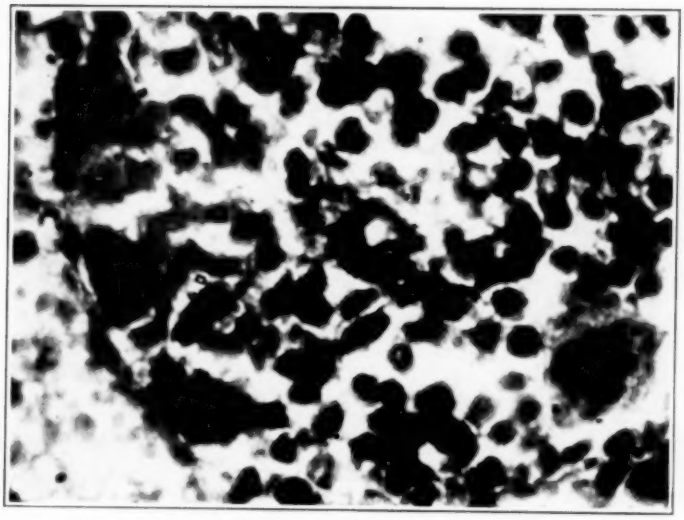


FIG. 1.—Megakaryocytes and transitional cell forms in the spleen.

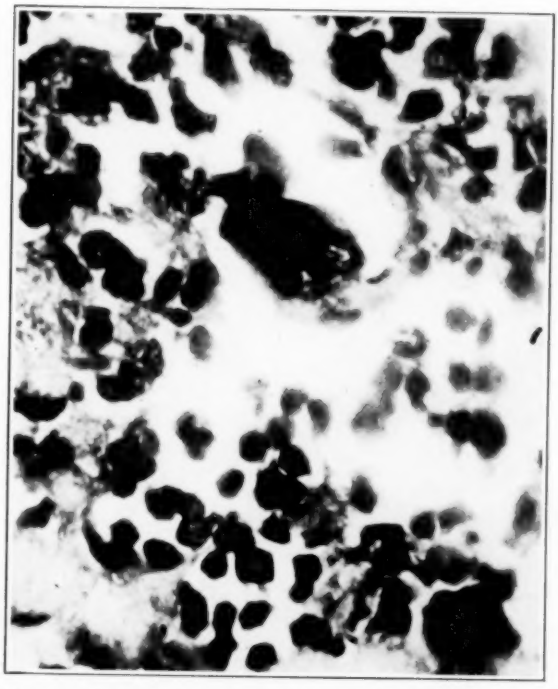


FIG. 2.—Megakaryocytes forming part of the cell lining of a sinus in the spleen.

FIG. 3.—Megakaryocytes in the dilated capillary lumina in the liver. Kupffer cell proliferation.

The existence of local relations between the occurrence of heterotopic megakaryocytes and extramedullary myeloid foci (Koerner,[7] Waterman,[15] Askanazy[19]) may be regarded as additional circumstantial evidence against the conception of an exclusive medullary origin and embolic distribution of these cells. It is known that in the normal spleen of the adult mouse megakaryocytes and myelocytes are often found coëxisting, *i. e.*, a condition persists during postembryonic life which is found in the human spleen and liver only during fetal life. Also an increase of megakaryocytes in the spleen and a reappearance of these cells in the liver and lymph nodes of the adult, and especially of the cancerous, white mouse is in general accompanied by an increase of the myeloid elements in the spleen (Hill[14]) and by the formation of smaller and larger myeloid foci in the liver and lymph nodes of these animals.

It has been argued that these heterotopic myeloid elements always originate from extravascularly implanted young blood cells derived from the bone marrow. But this conception completely disregards the numerous observations made in regard to the persistence of developmental potentialities in certain types of vascular cells during adult life (Maximow,[22] Askanazy[19]). In numerous livers of the carcinomatous mice the Kupffer cells were in a state of active proliferation and myeloid cell groups were found in the dilated lumina of the capillaries. There were also smaller and larger foci of reticular tissue with hematopoietic function located in close connection with the walls of the hepatic veins.

The numerical relations existing between the frequency and distribution of extramedullary megakaryocytes and the occurrence of heterotopic lymphoid and myeloid foci is illustrated in the following tabulation, extrasplenic megakaryocytes being represented by the numbers in parentheses.

	Splenic megakaryocytosis.				
	0	+	++	+++	++++
Lymphoid foci in 1 or several organs	6	5	41 (7)	21 (7)	14 (3)
Increased myeloid tissue in spleen	1	3	3	7 (1)	0
Myeloid foci in liver, lymph node and lung	1	3 (2)	11 (4)	28 (8)	13 (4)
No heterotopic lymphoid or myeloid foci	10	1	5	1	1

Beside this strong circumstantial evidence in favor of the local genesis of heterotopic megakaryocytes, the histologic examination of the spleen, liver and lymph node furnished confirmatory information of a more direct and conclusive character.

The spleens containing numerous megakaryocytes always showed evidence of more or less proliferative activity of the reticulum and reticuloendothelial cells. Usually there were in the pulp large numbers of round, moderately sized and fairly uniformly shaped cells which had a moderately large amount of cytoplasm and rather large vesicular nuclei with conspicuous interlacing chromatin

threads. These were regarded as free reticular cells. Cells of similar morphology were found in the sinuses together with evidence of proliferation of the lining cells. These cells were especially prominent in spleens with marked atrophic, fibrotic and amyloidotic changes, as they then frequently represented a predominant cell type on account of the simultaneous relative scarcity of lymphoid and myeloid cell elements. In spleens with lymphoid or myeloid hyperplasia the reticular cells were found intermingled with the respective mature and immature lymphoid and myeloid cell forms, the latter being easily recognizable by their ring-shaped nuclei.

Megakaryocytes were noted in varying numbers in the pulp and sinuses of the spleen. In some spleens they appeared to be more common in the subcapsular zone and in the neighborhood of the trabeculæ, where also accumulations of myeloid cells were most frequently found. They often occurred in small groups and clusters which were usually composed of giant cells in different stages of maturation intermingled with cells of an evidently transitional type (between reticulum and reticuloendothelial cells and well-developed young megakaryocytes). The mature megakaryocytes had a large segmented or nodulated nucleus of pyknotic, highly chromatic character and a large mass of an irregularly and usually not sharply contoured, eosinophilic cytoplasm. In less mature giant cells the nucleus was more compact and often indented on one side, resembling that of a monocyte in shape, and was surrounded by a more or less basophilic, distinctly outlined cytoplasm. Central rarefications were common in these nuclei. The cytoplasm was in general well and sharply outlined in the free cells and smaller in amount than that of the mature cell. This is apparently the form which Duesberg[20] has designated as "lymphoid" and which v. Boros and Korenyi[21] have called "megakaryoblast." In degenerating megakaryocytes, the nucleus seemed to have broken into several fragments. The outline of the cell was indistinct and highly irregular. Hyaline masses without nuclei or with a few chromatin granules represented completely degenerated giant cells, which were in some spleens quite numerous.

Many of the megakaryocytes found in the pulp seemed to be interconnected by delicate threads or compact plasmatic bridges with the adjacent reticulum cells, with which they apparently formed a synctial mass. Transitional forms of various stages between the reticulum cells and completely developed megakaryocytes were not rare, especially in the neighborhood of groups of megakaryocytes. During the early part of the transformation of a reticulum cell into a megakaryocyte there was only a diffuse general hypertrophy of the nucleus and cytoplasm of the reticulum cell noticeable. With the increasing swelling the cells showed a large, but rather compact nucleus, usually of round shape. Cells representing the next step in the megakaryocytic development of

reticulum cells resembled those described above as the "megakaryoblastic" form.

The endothelial cells lining the sinuses were apparently another source of megakaryocytic formation. Here enlarged and swollen cells projecting into the sinusoidal lumen were not infrequently observed. Sometimes 2 large swollen cells were found back to back, 1 protruding into the sinus, the other into the surrounding pulp. Cells possessing all the morphologic characteristics of megakaryocytes were often seen forming an integral part of the lining of sinuses. This type of development could be especially well followed in spleens with marked fibrotic and amyloidotic changes which emphasized the sinusoidal structure of the organ. The lymph follicles were always free from megakaryocytes.

Free forms of megakaryocytes of different degree of maturity were not only noted in the pulp and sinuses, but also in the lumens of the larger splenic veins. In 1 instance, 2 giant cells were found in the leukemic blood of a medium-sized vein passing through the pancreas. These observations indicated that megakaryocytes formed in the spleen can be the source of embolic megakaryocytosis in other organs.

In the liver the megakaryocytes were mainly located in the lumens of the sinusoidal capillaries. The cells seemed sometimes to be attached to the sinusoidal wall by plasmatic processes. This was often noted in livers which showed a marked proliferation of the Kupffer cells. The latter cells were swollen in some instances and protruded into the lumen, resembling in many respects the transitional forms found in the spleen. Extracapillary megakaryocytes were occasionally seen between the cells of perivascular myeloid infiltrations.

The megakaryocytes observed in the lymph nodes, which always contained myeloid foci, seemed to have the same genetic relations to the reticulum cells as those which have been described for the spleen.

The lung was, as has been stated above, quite often the seat of megakaryocytes. They were found lodged in the capillaries, bulging their walls into the alveolar lumen on both sides of the interalveolar septum. Their nuclei were always dark, pyknotic, markedly segmented and surrounded by little or no cytoplasm. The myeloid and lymphoid perivascular and peribronchial infiltrations were always free of these cells. The same observation was made in the myeloid and lymphoid foci in the kidney. The megakaryocytes found in the kidney were lodged in the glomerular capillaries.

These observations are important evidence in confirmation of the autochthonous origin of heterotopic megakaryocytes in white mice and support the claims of Custer,[13] Downey, Palmer and Powell[2] and Lignac[24] in regard to the derivation of these cells from both reticular and endothelial elements of the reticuloendothelial system.

The present investigation can add very little to the question of the causative mechanism of heterotopic megakaryocytic proliferation. The relatively frequent coëxistence of amyloidotic changes in the spleen and liver or both and extrasplenic megakaryocytosis suggests the possibility that toxic agents are also involved in the stimulation of megakaryocytic proliferation.

	Splenic megakaryocytosis.				
	0	+	++	+++	++++
Amyloidosis in spleen . . .	2	3 (2)	6 (2)	10 (3)	7 (1)
Amyloidosis in liver . . .	2	0	8 (5)	16 (5)	7 (3)

The numbers put in parentheses designate animals with extrasplenic megakaryocytosis.

While among 125 mice without amyloidosis 20 had an extrasplenic megakaryocytosis, 47 mice with amyloidosis showed this phenomenon in 16 cases.

The extent of the malignant growth as determined by the presence or absence of internal metastasis (heart, lung) had apparently no bearing upon the frequency and distribution of heterotopic megakaryocytes.

Conclusions. 1. In addition to extramedullary megakaryocytes of embolic origin (lung, kidney), autochthonous megakaryocytes also occur in various organs (spleen, liver, lymph nodes) of white mice with spontaneous mammary carcinomas.

2. This is supported by the following circumstantial and direct histologic evidence:

(*a*) The distribution of megakaryocytes in the various organs precludes their exclusively embolic origin from the bone marrow.

(*b*) The absence or relative rarity of traumatized megakaryocytes in the spleen, liver and lymph nodes refutes the assumption that these cells have been carried to these organs by way of the blood-vessels.

(*c*) The relations existing between the frequency and distribution of heterotopic megakaryocytes and of extramedullary myeloid foci support the probability of the local origin of heterotopic giant cells.

(*d*) Proliferation foci in the form of megakaryocytic clusters in the spleen and transitional cell forms between reticulum and reticuloendothelial cells and megakaryocytes in the spleen, lymph nodes and liver point to the local genesis of these cells.

REFERENCES.

1. Petri, S.: Fol. hæmatol., **37**, 129, 1928.
2. Downey, H., Palmer, M., and Powell, L.: Ibid., **41**, 55, 1930.
3. Aschoff, L.: Virchow's Arch. f. path. Anat., **134**, 11, 1893.
4. Lubarsch, O.: Ibid., **151**, 546, 1898; Handb. d. spez. path. Anat. u. Histol., Berlin, J. Springer, vol. **1**, 1927.
5. Goroncy, G.: Virchow's Arch. f. path. Anat., **249**, 357, 1924.

6. MacCallum, W. G.: A Textbook of Pathology, 4th ed., Philadelphia, W. B. Saunders Company, 1928.
7. Koerner, K.: Virchow's Arch. f. path. Anat., **259**, 617, 1926.
8. Naegeli, O.: Ber. d. deutsch. path. Gesellsch., **16**, 154, 1914.
9. Barth, H.: Virchow's Arch. f. path. Anat., **256**, 693, 1925.
10. Morawitz, P., and Denecke, K.: Mohr-Staehelin, Handbuch der Inneren Medizin, 2d ed., Berlin, J. Springer, vol. **4**, 1926.
11. Schridde, F.: Anat. Hefte, **33**, 1, 1907.
12. Kuczinski, M. H.: Virchow's Arch. f. path. Anat., **234**, 300, 1921.
13. Custer, R. P.: Ibid., **288**, 212, 1933.
14. Hill, F. McC.: Cancer Res., **14**, 325, 1930.
15. Waterman, N.: Frankf. Ztschr. f. Path., **44**, 541, 1933.
16. Jaffé, R. H.: Beitr. z. path. Anat. u. allg. Path., **68**, 224, 1921.
17. Simonds, J. P.: J. Cancer Res., **9**, 329, 1925.
18. Fischer-Wasels, B., and Buengeler, W.: Roux Arch., **112**, 184, 1927.
19. Askanazy, M.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, J. Springer, vol. **1**, 1926.
20. Duesberg, R.: Ztschr. f. klin. Med., **112**, 626, 1930.
21. v. Boros, J., and Korenyi, A.: Ibid., **11**, 697, 1931.
22. Maximow, A.: Arch. Path., **4**, 557, 1927.
23. Siegmund, H.: Verhandl. d. deutsch. path. Gesellsch., **19**, 114, 1923.
24. Lignac, G. O.: Krankheitsf., **9**, 403, 1932.

LEUKOCYTOSIS AFTER PARENTERAL INJECTION OF LIVER EXTRACT.*

By Ovid O. Meyer, M.D.,
William S. Middleton, M.D.,
and
Ethel M. Thewlis,
Madison, Wis.

(From the Department of Medicine, University of Wisconsin.)

Oral ingestion of whole liver is known to produce an increase in the leukocytes of the blood as well as other formed elements in patients with pernicious anemia (Murphy, Monroe and Fitz[1] and Minot and Murphy[2]). Murphy[3] noted that a sharp increase in the leukocyte count follows within a few hours, intravenous or intramuscular injection of liver extract in patients with pernicious anemia. Recently Powers, Murphy and Humphreys[4] found that a leukocytosis could also be produced in normal individuals by the injection of concentrated liver extract (Lederle). This leukocytosis, which was usually maximal in 6 or 7 hrs., was accompanied by an increase in neutrophils, both in total number and percentage. These workers suggest the possible value of parenteral liver extract in the treatment of some patients with persistent leukopenia and Foran, Sheaff and Trimmer[5] have treated 5 patients

* This study supported in part by a grant from the Wisconsin Alumni Research Foundation.

suffering from malignant neutropenia by means of parenteral and oral liver extract with apparent good results.

It was deemed desirable to compare the leukocytosis produced by liver extract injected intravenously and intramuscularly both in normal and in abnormal individuals. Furthermore, it was hoped by this study that the origin of the leukocytosis might be elucidated. It is claimed that after epinephrin administration, the leukocyte increase is due to splenic contraction. If this were found to be the case after liver extract administration, its value therapeutically in this field would probably be much less and its use less logical than if the bone marrow were actually stimulated to increased production. A recent report of Miller and Rhoads,[6] published as this work was being completed, suggests that this factor of splenic contraction is important. They noted increase in all formed elements of the blood, including the leukocytes, after the intravenous injection of liver extract, to a patient with anemia and splenomegaly. The increase in leukocytes, which is of primary interest here, was noted within 20 min. after the injection of the extract. Concurrent with this leukocytic increase, the spleen was observed fluoroscopically to be greatly contracted. Intramuscular injection of adrenalin gave results comparable to those with liver extract. A control patient without splenomegaly had no increase in the leukocytes or other formed elements in the blood stream under the same experimental conditions. Peculiarly, when eserin was injected intramuscularly in this same patient with splenomegaly, there was no peripheral increase in the formed elements of the blood although splenic contraction of a slower and lesser degree than with liver extract and adrenalin occurred.

Methods. In general, the methods of Powers, Murphy and Humphreys[4] in their study on normal individuals have been followed save for slight modifications which will be noted in the description and graphs below.

Blood counts were made over 3-day periods. On the 1st and 3d days all counts were started at 9 A.M. and continued at 11 A.M. and 2 and 4 P.M. These days served as the control periods, while the 2d day was the experimental day in each instance. On this 2d day, blood was taken for a count at 8.55 A.M., the liver extract was injected at 9 A.M.; 20 min. later a 2d count was made, a 3d at 10 A.M. and then hourly until 7 P.M. Exceptionally a count was also made at 8 P.M.

Each count was done in duplicate,* using the same 2 pipettes and same hemacytometer throughout the 3 days of each individual experiment. (In 1 experiment 1 of the pipettes was broken, necessitating the use of another set of 2 for the remaining counts of that experiment.) Two counts were made from each pipette, *i. e.*, 1 on each side of the hemacytometer, the 4 large corner squares being counted each time. Thus, each count reported represents the average of 4 counts. Occasionally there was a wide variation in the counts from the 2 pipettes, but ordinarily not. The average discrepancy between the highest and lowest counts was 12%,

* Blood for each count was taken from a prick in the ear into standard 1 to 11 pipettes, diluted 1 to 20, shaken for 3 min. and counted at once in a Levy counting chamber. The pipettes and the counting chamber were certified by the U. S. Bureau of Standards.

with a range for individual experiments between 9 and 15%, the highest percentage error occurring in the patients with the lowest leukocyte counts.

Coverslip smears were stained with Wright's stain and the differential counts were made of 200 cells in each instance. Schilling counts were done on 2 or more of the smears of the control period before liver extract was given, and on 2 or more during the period of high leukocyte counts in each reported experiment in order to ascertain whether or not there was an increase in young neutrophil cells in the peripheral blood.

Concentrated liver extract (Lederle), in 3-cc. doses, was given in each experiment; but when administered intravenously it was diluted in normal saline to a volume of 15 cc. The intravenous injections were made during a period of 5 to 10 min. into a vein in the antecubital fossa and the blood pressure, which usually but not invariably fell moderately, was taken repeatedly during this procedure. Intramuscular injections were made into the buttock.

One of us served as a normal control, and in this case, usual activities were carried out during the 3-day experimental period. A 2d normal was a patient without demonstrable disease. Two others were recuperating from operations for inguinal hernia done more than a week before. They were, of course, afebrile and for the present purpose might be considered as normal. These 3 patients were kept in bed during the experiments but had their meals regularly. Temperature readings were made at 8, 12, 4 and 8 o'clock on these 3 subjects on the day of the liver injections and 8 and 4, or at the same 4 periods, during the control days.

Results. Observations on the normal individuals after the intramuscular injection of liver extract confirmed the results of Powers, Murphy and Humphreys. A typical result though not the most striking is shown in Fig. 1. For comparison, in this same figure is shown the leukocytosis produced by the intravenous administration of liver extract to this same subject 2 days before.

The sharper and more prompt but less well sustained rise in the number of leukocytes after the intravenous injection is obvious. This was a consistent observation in the 3 normal and 1 abnormal subjects that received the extract intravenously. The maximal leukocyte count was reached 3 hr. after the intravenous injection, whereas, when the extract was administered intramuscularly, the highest count was attained only 5 or more hours after the injection. The increase in the neutrophils paralleled the rise in total leukocytes and there was also a relative increase in neutrophils. This patient had temperature elevation to 99.4° F. in the afternoon both after intravenous and intramuscular injections, but no subjective or objective signs of a marked reaction. Only 1 of all the subjects had a distinct reaction with a moderately severe chill and a febrile reaction to 100.4° F., 1¼ hr. after the extract was administered intravenously. His leukocyte count rose from an average control level of 9000 to 15,000.

In none of the normal individuals was there a demonstrable shift to the left in the Schilling counts.

Results in a Patient With Chronic Leukopenia. Case 1.—The patient, G. C., a white woman, aged 30, had recovered from a severe neutropenia, with daily high fever, at times exceeding 104° F., and lasting more than

a week. The total white count had been as low as 250, with 9% neutrophils, and at one time with a count of 400 there had been 2% neutrophils. She had been treated with pentnucleotid during the acute stage of serious neutropenia; but at the time the liver extract was administered for this experiment she had received none for more than 3 weeks. The white count for more than a month before the experiment had been persistently low, usually ranging between 2000 and 5000, with a relative neutrophil count of 50% or more.

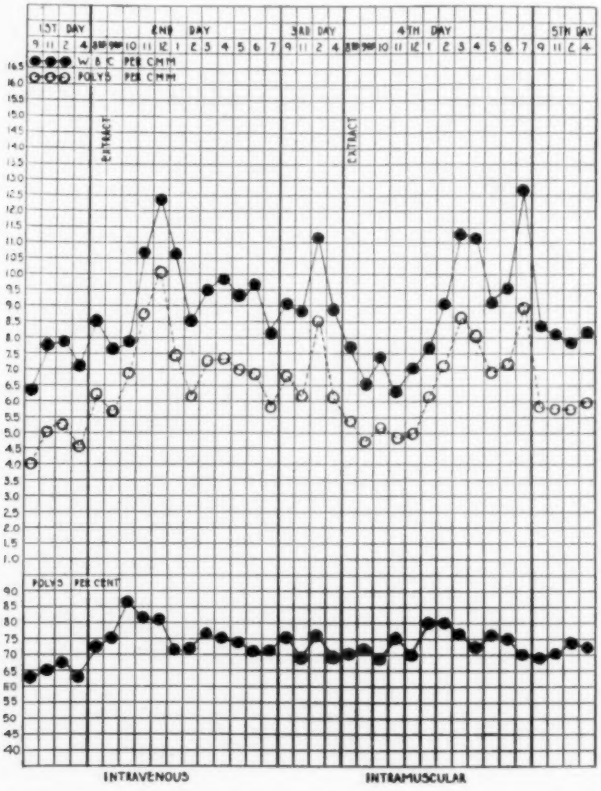


FIG. 1.—A comparison of the effect upon the leukocytes of intramuscular and intravenous administration of liver extract to a normal subject.

The experimental routine described above was followed; the liver extract (3 cc.) was administered intramuscularly at 9 A.M. on the 2d day. The patient was in bed throughout the period of the experiment. The result is shown in Fig. 2.

The response of the leukocytes resembles that of the normal shown in Fig. 1. A fall in the leukocyte count occurred 20 min. after the injection, followed by an increase above the basal level of the control periods. In this case the basal level is low and the maximum leukocyte count is not great; however, the actual level at 2 P.M., when the peak was attained, is 77% above the average of the control counts of the preceding day and 80% above the 2 P.M. count of the preceding day. An elevation in the total

and relative neutrophil counts is also similar to that of the normals. In this case, at 6 P.M. there was a second sharp rise of leukocytes to above 7000. This late rise was also observed at 7 P.M. in the experiment of Fig. 1 after the intramuscular injection of the extract. This 2d elevation of the leukocyte count was not a consistent finding, however, and no explanation for its occurrence is offered.

This experiment shows clearly that it is possible to elevate at least temporarily, a persistently low white count by injection of this

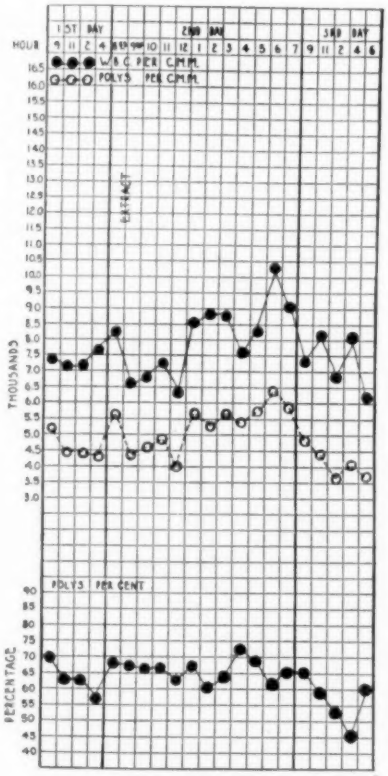


FIG. 2.—The effect of the intramuscular injection of liver extract upon the leukocyte count in a patient with a peristent leukopenia.

concentrated liver extract. Of course, this was observed on a single patient and a determination of the possible therapeutic efficacy of liver extract for this purpose requires further tests upon similar patients. Powers and his associates report that in their series one of the subjects developed influenza and with it a leukopenia during the period of observation. The response to the liver injected was nevertheless similar to that of the normal subjects in the temporary leukocytosis with total and percentage increase in neutrophils.

Effect of Liver Extract Before and After Splenectomy. CASE 2.—E. G., a well-developed, well-nourished white male, aged 38, was admitted to the hospital complaining of weakness. Save for marked pallor and a firm spleen, palpable 3 cm. below the costal margin, there was little of note on physical examination. Laboratory examinations on admission showed a hypochromic anemia, hemoglobin, 48% (Tallqvist), and red cells, 4,600,000, a persistent leukopenia with an approximately normal differential count. Fragility of the red cells was normal. Icterus index was 6; there was free acid in the aspirated gastric contents. Gastro-intestinal Roentgen rays revealed no abnormality. A diagnosis of Banti's disease was made and this was confirmed after operation by pathologic section and microscopic examination. Large doses of iron were administered, but liver was omitted. Shortly before the liver extract was given for the first experiment, the red cell count was 4,930,000 and the hemoglobin 55%.

Concentrated liver extract (3 cc. in 12 cc. of normal saline) was given at 9 A.M. There was some flushing of the face and increase in pulse rate during the injection and the systolic blood pressure rose from 130 to 146. Usually with intravenous injection of this extract a moderate fall in blood pressure occurred, but not in this instance. The leukocyte response to the injection was typical again with fall of the white cell count from 6700 at 8.55 A.M. to 4325 at 9.20 A.M. Subsequently there was an increase to a maximum of 8650 at 12 NOON. This level was 40% higher than the average of the 4 counts (6150) of the day preceding the extract administration, and as the average of the 11 A.M. and 2 P.M. counts was 5450, the increase over the level for a similar period of the day was still greater. There was also an increase in the percentage of neutrophils.

The 3d day was a control period for this experiment and also the 1st control day for a 2d experiment, when liver extract was injected intramuscularly. The counts this day were lower than the day preceding the intravenous injection. The response to the intramuscular injection of liver extract is shown in Fig. 3. Here the early leukopenia usually observed was slight and delayed. The increase in total leukocytes from an average level of 4181 of the control day to 8312 at 3 P.M. (an increase of about 100%) and in the neutrophils is obvious. In this experiment, and in no other, the Schilling counts showed a significant shift to the left, the "stab" cells were increased from 4.5% before the intramuscular injection to 13.5% when the leukocytes were most numerous. In addition, at this latter period there were 3.5% metamyelocytes, whereas there had been none before.

Shortly after these experiments, a splenectomy was done. Three weeks after this operation, when the red cells numbered more than 5,000,000 and the hemoglobin was 70%, liver extract was again administered intramuscularly (Fig. 3). The basal level of the white cells was higher after splenectomy, and the response to liver extract more striking. The total count, when maximal, was 71% higher than the average of the control counts of the previous day. This experiment was repeated twice, once the 2d day after this reported experiment and then again 4 days after the 2d. As the results in these 2 experiments were quite similar, only the latter is shown in Fig. 4.

The leukocytosis here was slight as compared to the first experiment following splenectomy, but still evident. Interestingly, after showing a tendency to fall, high counts were recorded at 6 P.M., 9,300 and leukocytes 10,400 respectively, for these last 2 experiments. This patient was afebrile for days before and after each experiment, but at noon on the day of intravenous injection, the temperature was 99.6° F. and on the day of the intramuscular injection before splenectomy 99.2° F. at 4 P.M. The maximal temperature of the 3 experimental periods after splenectomy was 99.4° F., 99.2° F. and 99° F. on the respective days of the intramuscular injections.

CASE 3.—B. M., a white woman, aged 46, was admitted to the hospital because of weakness. Important findings on physical examination were pallor, icterus and an enlarged spleen, which extended 8 cm. below the costal margin or to below the umbilicus. Laboratory examinations on admission included a red cell count of 3,400,000—reticulocytes 16.7% and hemoglobin 62% (Tallqvist). The erythrocytes began to hemolyze in 0.67% salt solution. Gastric analysis showed the presence of free hydrochloric acid. A diagnosis of familial hemolytic icterus was made and a splenectomy was advised.

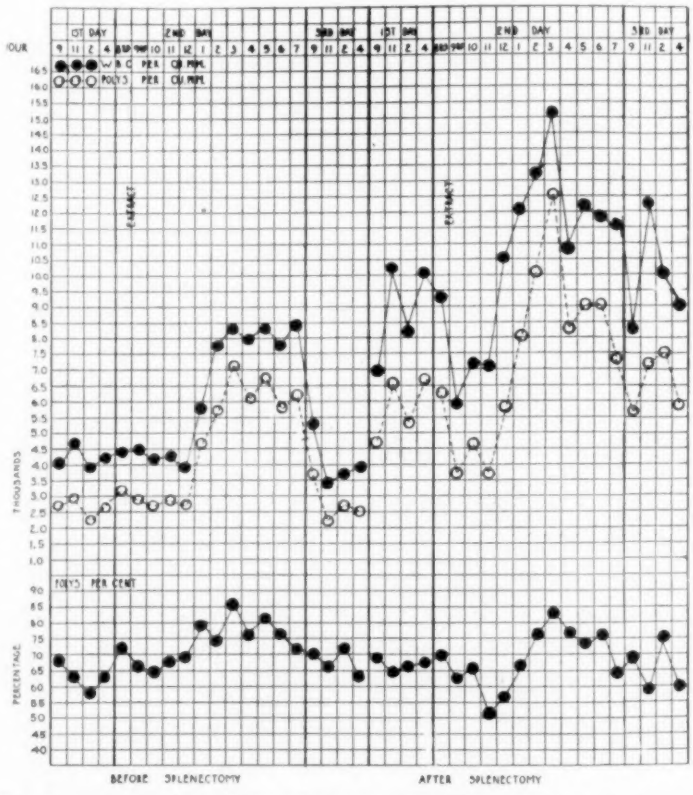


FIG. 3.—A comparison of the effect upon the leukocytes of the intramuscular administration of liver extract to patient (E. G.) with Banti's disease, before splenectomy and after splenectomy.

Before splenectomy, after the usual control period, liver extract (3 cc.) was administered intramuscularly and blood counts were done as in the other experiments. This study was repeated 17 days after splenectomy. The patient was kept in bed during both experimental periods until after the last count was done each day. Meals were taken at the regular hours, 7.30 to 7.45 A.M., 12 NOON and 5.45 to 6 P.M. The day of liver extract injection before splenectomy this patient's temperature was highest at 4 P.M., being 99.2° F. The day of the injection after splenectomy, the temperature was not above 98.6° F.

The effect of liver injection upon the white cell count before and after splenectomy is shown in Fig. 5. Because of continued rise in the white cell count before splenectomy until 7 P.M., an 8 o'clock count was made on the day of the injection, and a 6 o'clock count on the day after because of the 4 o'clock elevation on the control days.

Liver extract was again administered intramuscularly the 2d day after the postsplenectomy injection. Thus the 3d control period shown on Fig. 5 represented also the 1st control day for this 2d experiment. Again leuko-

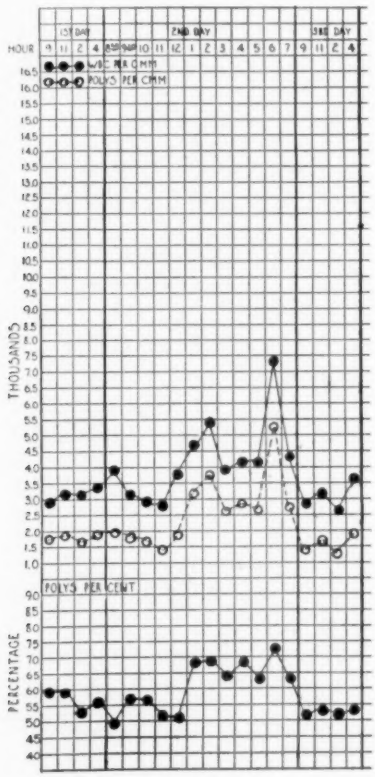


FIG. 4.—The effect of repetition of administration of liver extract to patient (E. G.), after splenectomy.

cytosis followed, reaching a height of 14,675 at 3 P.M., 6 hr. after the injection. The white cell count at 8.55 A.M., just before the extract was injected, was 8687. It should be noted that at the time of these experiments after splenectomy, the red cell count was 4,065,000 and the hemoglobin 80%. The fragility of the red cells was normal.

Particular attention is directed to the sharp fall in the number of leukocytes noted both before and after splenectomy when the count was taken 20 min. after the injection. In the experiment before splenectomy, the leukocyte rise commenced at about the usual time but the progression to a peak was slower than usual, the

summit not being attained until 7 P.M., 10 hr. after the injection. The percentage increase in neutrophils is more striking after splenectomy. Schilling counts both before and after splenectomy showed no increase in young cells over the normal numbers present before the injection of liver extract.

Discussion. These results, both for the normal and abnormal subjects, were quite pronounced and consistent. The trend of the leukocyte counts after the injection of this liver extract was similar

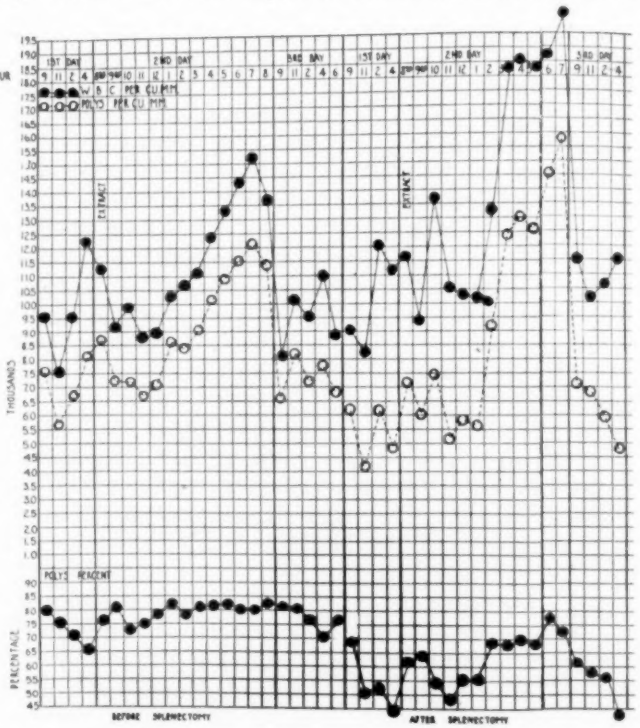


FIG. 5.—A comparison of the effect upon the leukocytes of intramuscular injections of liver extract in a patient with familial hemolytic icterus, before and after splenectomy.

in each case. The findings of Powers, Murphy and Humphreys[4] were thus confirmed.

In each subject the conditions of activity, food intake and other extraneous factors were comparable during the 2 control days and the experimental day. Caution was exercised in this matter for it was appreciated that many factors might alter the leukocyte count appreciably. The administration of various drugs, particularly the injection of foreign proteins, will produce leukocytosis, although Murphy[3] noted none after the intramuscular injection of aolan. Drug administration that might produce an increase in

leukocytes was avoided in the subjects under study, and Powers and his associates report that this liver extract (Lederle) has no foreign protein or infinitesmal amounts present. However, whether or not small amounts of protein exist is not of paramount importance in this investigation and no claim is made that leukocytosis cannot be produced by other methods.

In all of these experiments the liver extract was injected at 9 A. M., and thus when given intramuscularly, the maximum leukocytosis occurred in the middle or late afternoon. It was not thought necessary to administer it earlier so as to produce the leukocytosis earlier in the day, for when the extract was given intravenously, the maximum leukocytosis which was equal in degree occurred at 12 o'clock rather than at 3 or 4 P.M. Thus, the increase in leukocytes cannot be explained by a physiologic afternoon rise such as Shaw[7] describes. Furthermore, Powers[4] and his associates found that when the extract was injected intramuscularly at 5 A.M., instead of 9 A.M. the maximal response which was of similar degree occurred at 11 A. M. At this hour, according to Shaw,[7] the leukocyte count is normally at a low ebb. In view of these experimental results, and because of care in excluding extraneous factors, it is our belief that the leukocytosis produced in these experiments was due to the injection of liver extract and was neither physiologic nor due to some agent other than the injected material.

The patient, E. G., with early Banti's disease and the patient with hemolytic icterus, B. M., had splenomegaly. The spleen was not very large in the first case, therefore this case will be ignored in the present discussion. However, in the case of B. M., the spleen measured approximately 22 by 13 by 9 cm. after removal and thus was probably comparable in size to the spleen in the case of Miller and Rhoads.[6] The counts in their patients were done within 20 min. after the intravenous injection of liver extract, at which time there was an increase in the number of leukocytes as well as other formed elements of the blood. This early increase in white cells was not noted in our patient with splenomegaly nor in any other of the normal or abnormal individuals, whether the liver extract was given intravenously or intramuscularly. Instead, a decrease in the number of leukocytes was the usual rule 20 min. after the injection. This early decrease in leukocytes may possibly be explained by redistribution of the cells in the blood stream. The fact must not be overlooked that Miller and Rhoads used the liver extracts of other manufacturers than that which was used in this study. The results obtained after splenectomy in both E. G. and B. M. eliminate the possibility that the increase in leukocytes in the peripheral blood stream produced after the administration of this particular liver extract is due to splenic contraction. Furthermore, it very strongly suggests that the leukocytosis produced in the experiments on the normal individuals of the Powers, Murphy and Humphreys'[4]

series and of this group was not due to splenic contraction. Consequently, it is possible that the effect may be due to actual stimulation of the bone marrow, directly or indirectly. Of course, the fact that splenectomy does not effect any change in the response to parenteral injections of liver extract does not rule out the possibility of hepatic or splanchnic responses which have been considered in this relation. The possibility of the existence of accessory spleens in both E. G. and B. M. is not overlooked although this is unlikely. Furthermore, it would seem improbable that an organ the size of the ordinary accessory spleen could produce significant changes in the leukocyte count.

In only one of the Schilling counts, in the case of E. G. before splenectomy, was there noted a demonstrable shift to the left. This was when liver extract was injected 2 days after a previous injection. However, it is possible to stimulate bone marrow with the production of leukocytosis of short duration without calling forth young neutrophils into the peripheral blood stream. That young cells did appear however in 1 case, after leukocytosis had been induced just 2 days before, adds further strength to the belief that the leukogenetic centers in the bone marrow were stimulated by the liver extract.

Since liver extract apparently stimulates bone marrow, force is added to the suggestion of Powers and his associates that it "might be utilized clinically in the treatment of patients with chronic sepsis and a persistently low level of leukocytes." Possibly it also lends a measure of support to the therapy of Foran, Sheaff and Trimmer,[5] in agranulocytic angina. However, the etiologic factors and the status of the bone marrow in this disease demand further clarification before any positive statement can be made in this direction.

Summary and Conclusions. 1. The parenteral administration of concentrated liver extract (Lederle) was ordinarily attended by by an early fall in the white cell count and a constant subsequent leukocytosis with increases in total and relative numbers of neutrophils in 4 normal and 3 abnormal individuals.

2. The maximal leukocyte count was usually attained 3 hr. after the intravenous injection of the extract and 5 hr. or later after the intramuscular injection. After the intramuscular injection the rise, though less prompt, was better sustained.

3. In a patient with chronic leukopenia there was an increase in leukocytes to a maximum of 73% above the control period level.

4. In a patient with Banti's disease with leukopenia, leukocytosis was produced repeatedly by the parenteral injection of liver extract both before and after splenectomy. Also, a shift to the left in the Schilling count occurred on the occasion of an intramuscular injection before splenectomy. This was 2 days after the intravenous administration of the same extract.

5. Leukocytosis also occurred before and after splenectomy in a patient with familial hemolytic icterus.

6. Since leukocytosis can be produced by the intramuscular injection of this concentrated liver extract after splenectomy, it would appear that this substance does not produce the increase in the leukocytes by inducing splenic contraction, but possibly by a stimulation of the bone marrow, directly or indirectly.

7. The administration of liver extract to induce an elevation in the white count, at least temporarily, is logical. Its efficacy and limitations will be established by a thorough clinical trial.

BIBLIOGRAPHY.

1. Murphy, W. P., Monroe, R. T., and Fitz, R. J.: J. Am. Med. Assn., **88**, 1211, 1927.
2. Minot, G. R., and Murphy, W. P.: Ibid., **89**, 759, 1927.
3. Murphy, W. P.: Ibid., **98**, 1051, 1932.
4. Powers, J. H., Murphy, W. P., and Humphreys, K.: J. Clin. Invest., **12**, 713, 1933.
5. Foran, F. L., Sheaff, H. M., and Trimmer, R. W.: J. Am. Med. Assn., **100**, 1917, 1933.
6. Miller, D. K., and Rhoads, C. P.: J. Clin. Invest., **12**, 1009, 1933.
7. Shaw, A. F. B.: J. Path. and Bact., **30**, 1, 1927.

SURGICAL ASPECTS OF PERNICIOUS ANEMIA WITH SPECIAL REFERENCE TO THE TREATMENT.

By R. G. Hahn, M.D.,
RESIDENT PHYSICAN, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Medicine of the Harvard Medical School.)

In 1924 Minot and Murphy developed their well-known treatment for pernicious anemia.[1] Adequate treatment may be defined as that amount of liver which induces a remission and maintains the patient in the best condition of health.[4,6,10] Whether the treatment is carried out by the oral,[4] intramuscular[7] or intravenous[3] administration of potent liver preparations from this point of view is of no consequence. Intravenous injections, however, do not yet possess the security that is present in the other methods.

It is well recognized that certain conditions such as undue fatigue, inadequate nutrition and mental anxiety[6] can delay and prevent the restoration of a normal red blood cell picture, even though adequate treatment apparently is given to the patient. The most important hindrances in the development and maintenance of a normal blood picture in a patient with pernicious anemia are blood loss and infection.[5,8] The surgical procedure sometimes necessary to eradicate these hindrances may be a major or a minor operation. The influence of these inhibitory factors and the rather frequent need for surgical intervention led us to review the cases of pernicious

anemia that had been operated upon at this hospital and ascertain how they tolerated the operation, the effect of the operation on the blood picture, and the subsequent condition of the patient.

Prior to 1925 (pre-liver treatment era) 8 cases of pernicious anemia were operated upon. Table 1 presents a brief tabulation of the particular phases of these cases with which this report is concerned.

TABLE 1.—HEMOGLOBIN AND RED BLOOD CELL COUNTS BEFORE AND AFTER OPERATION.

		Before operation.		Days after operation.	After operation.	
	Age.	Hb. %.	R. B. C. in millions.		Hb. %.	R. B. C. in millions.
Limits	32–59	50–75	1.07 to 3.36	1–15	25–65	1.00 to 2.61
Average	48	60	1.99	6	50	1.64

These 8 cases (4 males, 4 females) had a total of 9 operations: 2 splenectomies, 1 nephrectomy, 1 trephine of tibia and rib, 1 reamputation of leg, 1 cholecystectomy, 1 cholecystectomy and splenectomy, 1 repair of traumatic laceration of hand, wrist and neck, 1 rib resection for drainage of empyema. Before the operation, 5 cases had a red blood cell count less than 2,000,000 cells per cmm. The remaining cases had 2,000,000 erythrocytes per cmm. or more. After the operation 7 cases had a red blood cell count less than 2,000,000 cells per cmm.; the remainder were above 2,000,000. Ether anesthesia was used on 4 occasions, gas-oxygen twice and novocain 3 times. The average time for the operation was 1 hr.; the limits 20 min. to 2 hr. and 15 min. Four blood transfusions were given to 3 patients before the operation and 8 transfusions to 5 patients after the operation. The average amount of each transfusion was 450 cc. Three of the 5 patients that were transfused after the operation had been transfused before the operation. There were no striking changes in any of the red blood cell counts. One patient died 20 days after a cholecystectomy and another 40 days after repair of traumatic lacerations of hand, wrist, and neck. Five patients died 1 to 3 years after the operation in a relapse of their pernicious anemia. One patient could not be traced.

The number of these cases is small. No definite conclusions can be drawn from them, but they do furnish some information which can be compared with that obtained from those who came fortunately at the time designated as the liver treatment era. The following table, similar in outline to the first one, presents a tabulation of those cases that received liver.

TABLE 2.—HEMOGLOBIN AND RED BLOOD CELL COUNTS BEFORE AND AFTER OPERATION.

		Before operation.		Days after operation.	After operation.	
	Age.	Hb. %.	R. B. C. in millions.		Hb. %.	R. B. C. in millions.
Limits	32–70	60–106	2.75 to 5.74	1–15	50–95	3.25 to 5.26
Average	55	76	4.20	6	70	4.10

These 24 patients (14 males, 10 females) had a total of 31 operations. Before 8 of these operations the red blood cell count was less than 4,000,000 cells per cmm., in the remainder it was more than 4,000,000. After the operation 11 cases had less than 4,000,000 red blood cells per cmm., and the remainder had more than 4,000,000. The following table records the operation, the type of anesthesia used, the time interval since the operation and the patient's condition at that time.

TABLE 3.—RÉSUMÉ OF OPERATIONS AND FOLLOW-UP OF PATIENT.

Case No.	Operation.	Anesthetic.	Follow-up.	Condition.
1.	Hemorrhoidectomy	Ether	7 years	Good.
	Dilatation and curettage and radium implantation	Ether	6 years	Good.
2.	Explore chest abscess	Novocain		
	Resect 3 costal cartilages	Novocain	7 years	Good.
3.	Appendectomy	Ether	6 years	Good.
4.	Amputation of breast	Gas-oxygen	5 years	Good.
5.	Choledochostomy	Ether	4 years	Good.
6.	Herniorrhaphy	Spinal	3 years	Good.
7.	Facial repair of hernial scar	Spinal	3 years	Good.
8.	Hemorrhoidectomy	Spinal	2 years	Good.
9.	Herniorrhaphy	Novocain	2 years	Good.
10.	Hemorrhoidectomy and radical antrum	Spinal Cocain	2 years	Died 2 months after a cholecystectomy.
11.	Cervical amputation	Ether	2 years	Good.
	Apical abscess drained	Gas-oxygen	6 months	Good.
12.	Hydrocele excision	Spinal		
	Hemorrhoidectomy	Spinal	2 years	Good.
13.	Hemorrhoidectomy	Spinal	1 year	Good.
	Cervical amputation with ant. and post. colporrhaphy	Spinal		
14.	Cholecystectomy	Avertin	1 year	Fair.
15.	Hemorrhoidectomy	Spinal	1 year	Good.
16.	Excision carbuncle	Gas-oxygen	1 year	Good.
17.	Hysterectomy and removal of adnexa	Avertin	1 year	Good.
18.	Hemorrhoidectomy	Novocain	1 year	Good.
19.	Dilatation and curettage and radium implantation	Gas-oxygen	6 months	Good.
20.	Cholecystectomy	Avertin	5 months	Dead.
21.	Cholecystectomy	Gas-oxygen	4 months	Dead.
22.	Hemorrhoidectomy	Ether	3 months	Good.
23.	Hydrocele excision	Spinal		
	Suprapubic prostatectomy	Spinal	3 months	Fair.
24.	Resection of part of colon for carcinoma	Ether	3 months	Good.

Spinal anesthesia was used 11 times, ether 7, gas-oxygen 5, novocain 4, avertin 3 and cocain once. In isolated instances the novocain and avertin were reënforced with gas-oxygen and ether respectively. The average time of the operations was 1 hr. (10 min. and 4 hr. extremes). Whenever possible the operation was deferred until the patient's red blood cell count was within normal range. There were no deaths in this group that could be attributed directly to the operation.

Case Abstracts. CASE 10.—A man, aged 54, was operated upon for hemorrhoids and an infected left antrum. His blood picture was essentially normal both before and after the operations. He had been maintained on 4 ounces of liver pulp or 2 to 3 vials of liver extract daily for several months previously and this same régime was continued throughout his operations and postoperative periods. Two years after discharge he had a cholecystectomy. Neurological symptoms, that were already present, increased markedly. He developed a phlebitis and died from a cerebral embolus 2 months after the operation. An autopsy did not throw much additional light on his case except to confirm the diagnosis of pernicious anemia.

Case 21.—A male, aged 55, died 4 months after a cholecystectomy. Before the operation his blood showed a hemoglobin of 80% and an erythrocyte count of 4,220,000 cells per cmm. For more than a year he had been maintained on raw and cooked liver, and for the last few months on 2 to 3 vials of liver extract daily by mouth. During this time his red blood cell count remained about the same as that stated above. His immediate postoperative course was stormy, complicated by "shock" and marked weakness. The latter persisted for more than 2 weeks and his anemia progressed. On the 23d day after the operation his red blood cell count was 2,700,000 cells per cmm. This developed despite the intake of 4 vials daily of a known potent liver extract, which was started on the 4th postoperative day and 2 days later increased to 6 vials daily. At the time of discharge from the hospital (81 days after the operation) he had a red blood cell count of 4,230,000 cells per cmm. and a hemoglobin of 80%. The cause of his death was not ascertained.

Case 20.—A 56-year-old female, who responded well to liver extract given orally, had a relapse under treatment and developed neurological symptoms. An intravenous cholecystogram showed a non-functioning gall bladder. Following a cholecystectomy she had an uneventful convalescence; her red blood cell counts improved moderately. She continued her liver medication and was readmitted 4 months later. A trophic ulcer had become infected and she died 6 weeks after admission, 5 months after the cholecystectomy. A postmortem examination showed extensive thrombosis of the iliac veins and lateral sinuses apparently related directly to the infected trophic ulcer.[9]*

In this group liver treatment was resumed on an average of 2 days after the operation. Twenty cases received liver preparations orally and 11 intramuscularly. Raw liver pulp and (Lilly's) liver extract No. 343 (N. N. R.) were the preparations given orally. Nine cases received the former, 9 the latter, and 2 were given both preparations. They received 250 to 600 gm. of the liver pulp or the equivalent value of liver extract daily. Eleven cases were treated exclusively by Lederle's intramuscular liver extract, receiving 3 to 6 cc. daily for 1 to 3 days depending on the severity of their anemia and subsequently 3 cc. once a week until discharged.

Blood transfusion was used twice in this group of cases.

Case 14.—A 65-year-old woman had responded poorly to liver therapy. Her red blood cell count had not increased more than 500,000 cells per cmm. in 4 weeks. She had received 3 intramuscular injections of liver extract in the first 2 weeks and 6 vials of liver extract daily by mouth during the last 2 weeks. While on the ward she developed an acute exacerbation of a chronic cholecystitis. The day before the operation her blood showed a hemoglobin of 65% and an erythrocyte count of 2,750,000 cells per cmm. She was given a transfusion of 300 cc. of blood and a cholecystectomy performed under avertin anesthesia. On the 7th day after the operation she was started on 6 vials of liver extract daily by mouth. Her entire postoperative course was uneventful. Blood examinations on the 10th day after the operation showed a hemoglobin of 55%, red blood cell count of 3,456,000 cells per cmm., and on the 35th day 65% and 4,290,000 respectively. At present, 1 year after the operation, she is in fair condition and has taken liver irregularly.

* The reference is a complete report of this case.

The following case illustrates some contingencies that may develop when the patient is not treated adequately before and after an operation.

CASE 23.—A 70-year-old man had had symptoms of pernicious anemia for more than 8 years. He received adequate treatment and during the past year had been kept in good health and maintained a normal red blood cell count on one intramuscular injection of liver extract every 6 weeks. Two weeks after one of his injections he was operated upon for a hydrocele sac and an enlarged prostate gland. His normal blood counts seemed to be a sufficient indication to the surgeons that no treatment was needed for his pernicious anemia until the usual time for his next injection. Two days after his second operation his red blood cell count was 2,920,000 cells per cmm. Intensive treatment was instituted with amelioration of his weakness and anorexia. He developed marked ataxia and paresthesia of his hands and legs. Twelve cc. of liver extract were given intramuscularly during the next 3 days, and one injection of 3 cc. each week thereafter. Three months after the operation his red blood cell count was 4,750,000 cells per cmm., and his neurologic symptoms had improved moderately.

A total of 10 oral operations were performed in both these groups, dealing only with the removal of several teeth, root fragments, or both. None of the patients had any unusual reactions. The operations were done under gas-oxygen anesthesia or local novocain injections. None of these patients had erythrocyte counts below 3,000,000 cells per cmm. before the operation. Complete blood studies after the operation were lacking in most instances.

It is interesting to note that 12 of the 24 patients in the second group had had 27 operations previous to those indicated in Table 3. Of these operations, 21 were done prior to the liver treatment era. Of the 27 operations, 15 were major procedures (appendectomy, cholecystectomy, hysterectomy, salpingectomy, herniorrhaphy).

Discussion. Previous to the advent of liver therapy the treatment of pernicious anemia patients before and after operation consisted largely of blood transfusions. The tendency to spontaneous remissions made it extremely hazardous for any prophet except Father Time to evaluate the efficiency of a given method of treatment. Certainly the advantages of splenectomy have not become apparent and can hardly be considered as an adjunct in the treatment of this disease.[2] The advent of liver in the treatment has changed this aspect of the problem completely, and the utility of the various preparations now employed enables one to treat the patient adequately throughout the operative period. Intramuscular injections of liver extract have largely replaced at this hospital the oral preparations. The injections cause only slight discomfort and only minor reactions have been encountered.

In the first group of cases reported (those before the advent of liver therapy) many blood transfusions were used: in the second group (those after advent of liver therapy) only 2 transfusions were thought to be necessary. In the first group 5 patients died within 3

years after discharge from the hospital, and 2 died 20 and 40 days after the operation. In only 1 of these 8 patients could the operation be said to have been related directly to the mortality, and in this instance a complicating cardiac and renal insufficiency was the main cause of the death. These cases tolerated the operations very well. Their average erythrocyte counts were low and the slight reduction of the red blood cell count after the operation was enough to aggravate the existing anemia. Their postoperative course was no more subject to complications than that of similar cases without pernicious anemia. The numerous transfusions doubtless played a major rôle in aiding these patients to tolerate the operations so well.

In the second group the operations were deferred, if possible, until the red blood cell count was within normal range. If immediate surgical intervention was indicated, the operation was performed and the patient received intensive liver therapy, abetted by transfusion if necessary. Case 14, cited previously, was the only one in this group operated upon when the red blood cell count was low. If the hematologic response was unsatisfactory and a condition amenable to surgical treatment existed, operation was advised and carried out when the patient was in the best condition possible. Cases 1, 2 and 8 are examples of this situation. Adequate treatment over quite a long period did not bring their red blood cell counts entirely to normal. After the operation a normal erythrocyte count was established and maintained. A brief history of these cases follows.

Case 1.—A 42-year-old woman had had symptoms of pernicious anemia for 2 years. She responded well to treatment. Her erythrocyte count varied from 3.5 to 4.5 million per cmm. She had intermittently bleeding hemorrhoids and moderate menopausal bleeding. Since the operation her erythrocyte count has been consistently over 5 million. The treatment of her pernicious anemia has been the same since operation as it was previously.

Case 2.—A 63-year-old man was under treatment for a year for pernicious anemia. He made a good initial response but his red blood cell count remained in the vicinity of 3.5 million. He was operated upon for a tuberculous abscess of the chest wall. Within 2 months his count had risen to 4.5 million and has remained between that level and 5.5 million on practically the same amount of liver as he had taken before operation.

Case 8.—This man of 52 years had had symptoms of pernicious anemia for 2 months and responded well to treatment. He had intermittent bleeding hemorrhoids. Previous to operation his red blood cell count had averaged 4.5 million, decreasing to 3.5 million when he lost blood. After operation his red blood cell count reached and maintained consistently more than 5 million on the same, or equivalent, liver therapy as he had taken previously.

It is interesting to note the 3 mortalities. They had had cholecystectomies, 2 of which (Cases 20 and 21) were done in this hospital. The former has been presented. The latter did not improve and died 4 months after the operation with well advanced neurologic

changes. The 3d one (Case 10) was operated upon in another hospital and died 2 months after the operation. These 3 incidents cannot help but bring to mind the possible relationship between biliary and hepatic disease and anemia, particularly pernicious anemia.[11,12] The postoperative course in these 3 patients was uncomplicated in 1, "stormy" in another, and that of the 3d is not known. All 3 had moderate subjective neurologic symptoms, and in 2 of them these symptoms became progressively worse. In contrast to these, Case 14, one year after a cholecystectomy, had a red blood cell count of 3,500,000 cells per cmm. She did not feel well but had not followed her liver treatment faithfully.

Whether or not these deaths have any relation to the operation, the condition of the patient previous to the operation, or the method of treatment, we are not prepared to state. Satisfactory information has not been obtained of the treatment and clinical course either of Case 10 that had a cholecystectomy in another hospital, or of Case 21 that died after discharge from this hospital. It does not appear likely that the operation can be blamed or criticized. As far as can be determined there were no unusual differences in the general physical condition of these 3 patients and others who had operative procedures of equal magnitude.

In this review the presence or absence of neurologic symptoms was noted before and after operation. Exact information frequently was not given. Whenever it was noted these symptoms were practically always made worse by the operation and several times made their initial appearance soon after the operation. This was especially apt to occur when adequate treatment was not provided, or when a marked fall in the red blood cell count followed the operation (see Case 23 cited previously). Improvement in the red blood cell count is frequently, though not always, accompanied by a diminution in the neurologic symptoms. Although the cause of these central nervous system changes is not known, it is reasonable to assume that the anemia does not play a neutral or disinterested rôle. Possibly forced confinement in bed after surgical treatment may play some causative part.

Whether the liver was given intramuscularly or by oral administration did not appear to make any difference, provided an adequate amount was taken by the patient. The advantages of the intramuscular route are obvious. By this method a definite amount can be administered, and the treatment can be carried out regardless of the nature of the operation and of the type of anesthesia employed. The essential feature is to give an adequate amount of potent material.

Most of these patients were given iron (ferrous carbonate [U. S. P] or ferric and ammonium citrate [U. S. P.] 3 to 6 gm. daily), usually being begun in the convalescent period. The red blood cell counts were made 1 to 12 days before the operation (average 3 days).

Those recorded after the operation were done at 1 to 15 days (average 6 days).

These patients with pernicious anemia tolerate operative procedures very well. They do not seem to be subject to surgical complications any more than other patients. The type of anesthetic employed and the length of time that the operation required did not bear any relation to the complications or the end results. The definite impression that following an operation central nervous system symptoms may develop or be increased, if already present, certainly should be taken into consideration when the operation is not strictly necessary. The erythrocyte count tends to decrease after the operation, which apparently is not a result of blood loss. This can be greatly lessened and frequently obviated if treatment is given intensively before the operation and continued through convalescence. Sources of blood loss and infection frequently stand as barriers successfully preventing the attainment or maintenance of normal red blood cell levels. In those instances the eradication of these foci has a distinct therapeutic value and should not be neglected. The possible development of cord changes demands the fullest safeguard that can be provided, and at present this is intensive treatment during the pre-operative and postoperative periods.

Summary and Conclusions. A series of 32 cases of pernicious anemia that were operated upon is presented, with a discussion of the influence of the operation on their pernicious anemia and on the possibility of the development of central nervous system lesions. Many of these patients had sources of blood loss or infection which seemed to prevent the establishment or maintenance of normal red blood cell counts. The removal of these sources appeared to have a definite therapeutic value, as subsequent red blood cell counts showed an increase in the number of erythrocytes. Most of the cases received intensive treatment before the operation and during the postoperative period. One exception developed marked symptoms of central nervous system damage following the operation. It is our strong impression that surgical operations on patients with pernicious anemia have a definite tendency to precipitate or increase the development of neurologic symptoms. These can and should be guarded against by intensive liver therapy before and after operation.

Patients with pernicious anemia that are treated intensively before the operation and during the postoperative period tolerate surgical operations very well and are good surgical risks.

I wish to express my appreciation to Dr. William P. Murphy for his helpful criticisms and suggestions.

REFERENCES.

1. Minot, G. R., and Murphy, W. P.: J. Am. Med. Assn., **87**, 470, 1926.
2. Muller, G. P.: Surg. Clin. North America, **10**, 1377, 1930.
3. Castle, W. B., and Taylor, F. H. L.: J. Am. Med. Assn., **96**, 1198, 1931.

4. Beebe, R. T., and Lewis, G. E.: Am. J. Med. Sci., 1931, **181**, 796.
5. Sturgis, C. C., and Isaacs, R.: Ann. Int. Med., 1931–1932, **5**, 131.
6. Minot, G. R., and Castle, W. B.: Ibid., p. 159.
7. Murphy, W. P.: J. Am. Med. Assn., 1932, **98**, 1051.
8. Minot, G. R.: Ibid., 1932, **99**, 1906.
9. Harvey, E. A., and Murphy, W. P.: Ann. Int. Med., 1933, **6**, 1393.
10. Murphy, W. P.: Proc. Am. Therap. Soc., June 10, 1933.
11. Jones, N. W., and Thomas, M. J.: Am. J. Med. Sci., 1927, **173**, 526.
12. Wintrobe, M. M., and Schumaker, H. S., Jr.: Bull. Johns Hopkins Hosp., 1933, **52**, 387.

THE RELATION BETWEEN ORAL AND RECTAL TEMPERATURES IN NORMAL AND SCHIZOPHRENIC SUBJECTS.*

By Hugh T. Carmichael, M.D., C.M., M.S.,
clinical research psychiatrist, research service,
and
Forrest E. Linder, Ph.D.,
associate statistician, research service, worcester state hospital,
worcester, mass.

With the Collaboration of the Research Staff of the Worcester State Hospital.

(From the Worcester State Hospital and the Memorial Foundation for Neuro-endocrine Research, Harvard Medical School.)

Body temperature in man has been studied intensively since the latter half of the 19th century. Historical reviews have been presented by Wunderlich,[1] Pembrey[2] and by Woodhead and Varrier-Jones.[3] These deal with the development of thermometry in medicine, the introduction of the clinical thermometer, and the general acceptance by the medical profession of the value of a knowledge of body temperature in the diagnosis and treatment of disease. Wunderlich's classical work[1] played a major rôle in emphasizing the importance of studying body temperature.

Many investigations have been directed toward ascertaining the temperature in various parts of the body and the relations among these. Numerous studies have been made of the influence of such factors as exercise, food, sleep, climate, age, sex, disease, etc., on heat regulation. Reference to a large number of these may be found in the reviews noted above.

Several parts of the body are used in the determination of temperature. The axilla is generally so utilized in Europe and Great Britain. In this country the mouth is preferred. The rectum commonly serves as the site when temperature measurements are made in infants and children; but in recent years, clinicians have more and more frequently selected the rectum as the location in both adults and children.

* Submitted by Dr. R. G. Hoskins, Director of Research, The Memorial Foundation for Neuro-endocrine Research.

Physiologic and clinical researches frequently involve the determination of body temperature. Sometimes the results of oral measurements are reported; at other times rectal measurements. In dealing with psychotic subjects it is often necessary to make rectal rather than oral measurements because of uncoöperativeness. This causes difficulty when attempting to compare results with published reports in which oral temperature was measured.

There appears to have become widespread in this country among members of the medical profession and nurses the impression that the rectal temperature exceeds the oral by 1° F. Just how this has come about is difficult to explain. Numerous observers have pointed out that the difference between the temperature in the mouth and in the rectum may vary from 0° F to 2° F, or even more if taken immediately after exercise or in cold weather. Burton-Fanning and Champion[4] state that the rectal temperature is on the average 0.4° F higher than the oral and give the limits of variation as 0.0° F to 0.8° F. Wunderlich[1] notes the rectal temperature as 0.5° F to 2° F (on the average 0.7° F) higher than that in the mouth. Pembrey[7] gives the average difference between oral and rectal temperature, obtained from the results of several observers, as 0.72°. Bardswell and Chapman[6] give 0.9° at rest and 1.8° immediately after exercise as the difference. Reichert[7] says the mean rectal temperature is 0.18° to 1.8° higher than the mean oral temperature. Hewlett[8] states the difference as one degree and notes that this figure is increased when the mouth has been cooled. Burton-Opitz[9] gives the difference as 0.54°. Howell[10] apparently follows Pembrey[2] in giving the average oral temperature as 98.36° and the average rectal temperature as 98.96°. Macleod[11] says that the rectal temperature is usually about 1.8° higher than the oral. Wright[12] states that the rectal temperature is 0.50° to 0.75° higher than the oral and that it may be higher after exercise. It is clear that the general acceptance by physicians of one degree as the standard difference does not take proper account of the literature.

In many instances in clinical work no harm may be done by accepting 1° F as the standard difference. But in certain research problems it is necessary to know the nature of the relation of the two variables. It has seemed desirable, therefore, to investigate oral and rectal temperatures in order to determine more accurately the relationship between them. Along with investigation of this relationship, some points of general clinical importance and interest have been studied. The two groups of subjects used in the study enable a comparison to be made between normal subjects and those suffering from schizophrenia. In addition, observations on so-called "normal" body temperature have been made.

Methods and Materials. Simultaneous readings of oral and rectal temperatures were made in 25 hospitalized male schizophrenic subjects and in 24 normal male subjects, during December, 1932, and January, 1933.

For each subject readings were taken twice a day (for 12 nearly consecutive days), one between 8 and 9 A.M. and one between 4 and 5 P.M. This gave 24 pairs of simultaneous determinations for each subject. A total of 2352 observations were made.

The schizophrenic group ranged in age from approximately 17 to 45 years and was free from any detectable physical disease or deformities. The normal group consisted of apparently healthy physicians, research workers, and attendants, ranging in age from approximately 21 to 45 years. The degree of activity differed somewhat in the two groups. The patients were less active, were confined to the wards throughout the course of the study, followed a more regular routine of daily life, and rested ½ to 1 hr. before each reading was made. The "normals" were more active, many lived on the hospital grounds apart from the main buildings, none followed a regular daily routine, and immediately preceding the temperature readings they rested not at all, or only for a few minutes.

Before the experiment was begun the clinical thermometers, graduated in degrees Fahrenheit, were immersed simultaneously in water, the temperature of which was determined by a standard scientific thermometer. The average thermometer reading was computed for each of 12 tests and the discrepancy of each thermometer from this average tabulated. The greatest average discrepancy was 0.07°. The thermometers were paired on the basis of the average discrepancy so that 6 practically equivalent pairs were obtained. One pair was assigned to each subject. Therefore, all oral readings on any one subject were taken with a single thermometer and all rectal readings on that subject were taken with a matched thermometer.

All observations were made in well-heated rooms, with the subjects recumbent and fully clothed except for the time necessary to permit insertion of the thermometer in the rectum. The morning readings were made within an hour after breakfast and the afternoon readings within an hour before supper. For both oral and rectal readings the thermometers were in place for at least 10 min. In all instances care was taken to have the thermometers correctly placed in the mouth and inserted at least 5 cm. in the rectum. In the schizophrenic subjects it was necessary to keep constant watch to insure that the lips were tightly closed and that there was no manipulation of the thermometer with the tongue. If these requirements were not strictly fulfilled the time the thermometers were in place was extended—in some instances to as long as 20 min. Generally the coöperation was such that a reliable measurement could be made in minimum time.

Results and Discussion. For each subject the measurements of oral temperatures made in the morning and afternoon are grouped together (Table 1). The rectal readings are similarly grouped. An objection might be raised to this procedure as ignoring the diurnal variation in body temperature. However, as shown by Table 2, the difference between the mean oral as well as the mean rectal temperatures of morning and afternoon for schizophrenic subjects is only 0.14°. For "normals" these differences are 0.29° and 0.10°, respectively.

In contrast with these relatively minor differences are the results obtained in a supplementary study at a longer interval between readings. At 4 to 5 A.M. and 4 to 5 P.M. measurements were made on 61 schizophrenic subjects every day for 30 days; a second period of 30 days followed 2 months later; and a final 30-day period after

another 2 months[5]. Most of the patients used in the smaller group served also for the latter study. The average differences between the morning and afternoon readings for the 3 periods were 1.32°, 1.36°, and 1.32° (Table 3). These differences are large in comparison with those noted between the 8 to 9 A.M. and 4 to 5 P.M. readings.

TABLE 1.—AVERAGE ORAL AND RECTAL TEMPERATURES FOR "NORMALS" AND SCHIZOPHRENICS.

Individual means—"normals."	No.	Min.	Max.	Range.	Mean and standard error.
Oral	24	97.4	98.4	1.0	97.93 ± 0.06
Rectal	24	98.2	99.5	1.3	98.88 ± 0.07
Individual means—"Schizophrenics."					
Oral	25	97.6	98.8	1.2	98.25 ± 0.06
Rectal	25	98.2	99.5	1.3	98.79 ± 0.06
Mean differences—"normals"	24	0.42	1.79	1.37	0.95 ± 0.07
Mean differences—"Schizophrenics"	25	0.26	0.80	0.54	0.54 ± 0.03

TABLE 2.—MEAN MORNING AND AFTERNOON TEMPERATURES FOR "NORMALS" AND SCHIZOPHRENICS.

Standard Errors are Used.

	Oral.		Rectal.	
	A.M.	P.M.	A.M.	P.M.
Patients	98.17 ± 0.06	98.31 ± 0.06	98.72 ± 0.07	98.86 ± 0.06
Controls	97.80 ± 0.07	98.09 ± 0.06	98.81 ± 0.10	98.91 ± 0.08

TABLE 3.—AVERAGE MORNING AND AFTERNOON RECTAL TEMPERATURES FOR PERIODS OF 1 MONTH EACH IN 61 SCHIZOPHRENIC PATIENTS.

Standard Errors are Used.

	4 to 5 A.M.	4 to 5 P.M.	Difference.
I Period	97.5 ± 0.02	98.8 ± 0.03	1.32 ± 0.04
II Period	97.6 ± 0.03	99.0 ± 0.02	1.36 ± 0.03
III Period	97.7 ± 0.04	99.1 ± 0.03	1.32 ± 0.04

The mean difference of 0.95° between oral and rectal temperatures in the normal subjects would at first glance seem to bear out the impression of clinicians that the rectal temperature is about 1° higher than the oral. But it must be remembered that this is the average difference for the entire group; the average difference in individuals of the group ranged from 1.79° to 0.42°. The difference between oral and rectal measurements at any one time showed even more marked variation than the mean differences. In one normal subject the rectal temperature was 3.5° higher than the oral; in another the oral was 1.7° higher than the rectal. The graph in Fig. 1 indicates clearly how widely scattered are the differences in individuals and shows that even the bulk of the observations represents a wide range. It is obvious that the use of the mean difference of 0.95° as the standard by which to estimate the relationship of oral to rectal temperature of any given individual case is entirely unreliable.

In the schizophrenic group the mean difference is 0.54°. The average difference in individuals of this group ranged from 0.80° to

0.26°. In one subject on one occasion the rectal temperature was 1.8° higher than the oral; in another the oral reading was 0.6° higher than the rectal. The graph, Fig. 2, illustrates these findings.

Comparison of the figures obtained for the schizophrenics with the figures for the normal group reveals distinct differences. It has

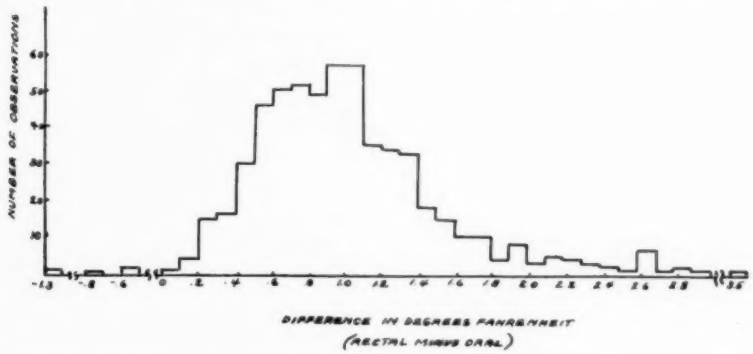


FIG. 1.—Variation of rectal minus oral differences in normal control subjects. Graph shows aggregate distribution of differences based on 24 simultaneous oral and rectal temperature measurements on 24 subjects.

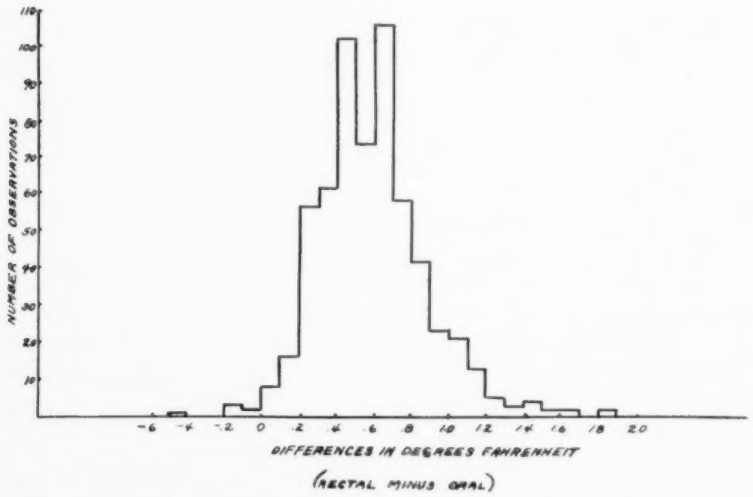


FIG. 2.—Variation of rectal minus oral differences in schizophrenic subjects. Graph shows aggregate distribution of differences based on 24 simultaneous oral and rectal temperature measurements on 25 subjects.

been pointed out in the description of methods and materials that the normal group was subjected to more varied conditions than the schizophrenic group. To what extent the smaller mean difference between oral and rectal temperatures in the patients was related

to the more constant conditions obtaining among them, and to what extent the difference may have represented a characteristic of the psychosis, these studies do not show. The problem is under further study.

Investigation of the correlations between the oral and rectal temperatures shows a striking difference between the normal subjects and the patients. In the normal group individual correlation coefficients range from $-.41$ to $+.91$, with an average of $+.56$. In some cases the rectal temperature tended to be low when the oral was high and *vice versa*, whereas in others the two varied together. In the schizophrenic group the range is from $+.20$ to $+.92$, with an average of $+.73$. This difference between the two groups may in part be evidence of the influence exerted by the greater variation of activity on the "normals." But even under the fairly constant conditions obtaining among the patients, the predictability of oral temperature from the rectal is of low degree. Among normal subjects the possibility of predictability becomes entirely illusory.

Detailed statistical analysis reported by us in another paper[13] shows that in comparing the figures for "normals" with those for schizophrenics one finds that there is greater variability shown by the "normals." In the case of the schizophrenics no distinction can be made between the oral and rectal temperatures as to relative reliability. In the "normals" the rectal temperatures seem to show greater stability than the oral. These results suggest that in dealing with individuals such as the normal group, who are subjected to varying conditions of activity and of external temperature, the rectal measurement is a more reliable source of information. In individuals like our schizophrenic group, who are restricted in activity and not exposed to variations in external temperature, both rectal and oral measurements seem to be of equal reliability. Studies by Hoskins and Sleeper[14] had suggested that abnormal variability of physiologic functions would be shown by the schizophrenics. This is not the case in the present study of body temperature.

Several authors state that hypothermia is a common finding in schizophrenia. Kraepelin[15] says, "Temperature is usually low, sometimes sub-normal, with occasional reversal and small range of the daily fluctuations." Bleuler[16] and Singer[17] make similar statements. Langfeldt[18] quotes several writers on this point, some of whom agree while others write of a rise of temperature for which no reason was found. Hypothermia was noted as a rather constant finding in the numerous studies of body temperature in mental and nervous diseases made in the latter half of the 19th century (Williams,[19] Wunderlich,[2] Zenker,[20] Snell[21]). It seems impractical to take the results of studies made on body temperature in the psychoses before the general adoption of the Kraepelinian classification for comparison with the results of our present study, as the schizophrenic (dementia precox) group was not separated from the

other psychoses. There is in recent literature practically no reference to body temperature in schizophrenia.

In this study the normal subjects had a lower mean oral temperature than the schizophrenics and essentially the same mean rectal temperature (Table 1).

In this country and in Europe, 98.6° has been generally accepted as the "normal" body temperature of the healthy individual. Clinical thermometers have a mark at this level, and on clinical charts a heavy line is found at 98.6°. In British countries 98.4° has come to be regarded as the "normal." This figure is derived, as Pembrey[2] has pointed out, from the observations of John Davy, and represents the mean of observations of oral temperature taken on himself chiefly during the active part of the day, with very few observations between midnight and early morning. Investigators in thermometry (Pembrey,[2] Wunderlich,[1] etc.) have pointed out that these figures by no means cover the facts.

Some recent writers have pointed out that to accept the figures 98.6° or 98.4° as the normal body temperature is wrong. Lyon and Wallace[22] found the mean axillary temperature in 250 non-febrile hospital patients confined to bed to be 97.2° at 7.00 A.M. and 97.45° at 7.00 P.M., with an average of 97.32°. They state that 98.4° is not the maximum reading above which the presence of fever may be assumed, and that it is inaccurate for patients confined to bed for long periods. Whiting[23] reports the mean oral temperature in 500 criminals as 98.37° and gives 98.38° as the mean for those prisoners apparently in perfect health. Paton[24] found in a study of the oral temperature in 108 healthy schoolgirls from 14 to 17 years of age that 75 per cent of the readings were below 98.4°. Rautmann[25] in a study of more than 1000 students from 18 to 22 years of age determined an average axillary temperature in males of 98.2°, with extremes of 96.4° and 100°; in females a fraction of a degree lower.

Our results as shown in Table 1 support the contention that 98.6° or 98.4° should not be regarded as the normal body temperature. These latter figures were supposed to represent the mean temperature in a healthy individual and do not make allowance for the regular diurnal variations, the degree of activity, the external conditions, or take into account the probability that there is a range within which the temperature may vary in different individuals in health. In the "normals" the mean oral temperature ranged from an individual mean of 96.9° to one of 98.4° in the morning, and from 97.5° to 98.5° in the afternoon. These figures do not show the extreme minimum and maximum values for any one reading in an individual, which are 94.6° and 100.2° respectively. Study of the figures given for mean rectal temperatures in the "normals" reveals similar findings, as do also the figures given for the schizophrenics. It must be pointed out that patients met in clinical practice are

seen under more variable conditions than our "normals," and therefore under such conditions greater temperature fluctuations than reported here may be observed.

Summary. A study of the relation between oral and rectal temperatures measured simultaneously in 24 normal and 25 schizophrenic subjects is reported.

The mean oral temperature was 0.95° lower than the rectal temperature in the "normals" and 0.54° lower in the schizophrenic group.

A low degree of predictability of oral temperature from the rectal temperature in the non-active schizophrenic group is shown by the correlations obtained. In the active normal group predictability becomes impossible.

The normal subjects individually showed more variability than did the individual patients.

In the normal subjects rectal measurements were apparently more reliable as an indication of body temperature. Oral and rectal readings were apparently equally reliable for this purpose in the patients.

The normal subjects had a lower mean oral temperature than the patients and essentially the same mean rectal temperature.

The difference in the figures for the two groups may be in part accounted for by the greater activity of the "normals." The suggestion is made that the heat regulating mechanism in the schizophrenic subjects may be different than in the "normals."

REFERENCES.

1. Wunderlich, C. A.: A Manual of Medical Thermometry, London, New Sydenham Society, 1871, **49**, 1.

2. Pembrey, M. S.: Text-book of Physiology (Schafer), Edinburgh, Young G. Pentland, 1898, **1**, 785.

3. Woodhead, G. S., and Varrier-Jones, P. C.: Lancet, 1916, **1**, 173.

4. Burton-Fanning, F. W., and Champion, S. G.: Ibid., 1903, **1**, 856.

5. Hoskins, R. G., *et al.*: Arch. Neurol. and Psychiat., 1933, **30**, 388.

6. Bardswell, N. D., and Chapman, J. E.: Brit. Med. J., 1911, **1**, 1106.

7. Reichert, E. T.: An American Textbook of Physiology (Howell), 2d ed., Philadelphia, W. B. Saunders Company, 1903, **1**, 467.

8. Hewlett, A. W.: Pathological Physiology of Internal Diseases, 2d ed., New York and London, D. Appleton and Co., 1924, p. 477.

9. Burton-Opitz, R.: Elementary Manual of Physiology, 3d ed., Philadelphia, W. B. Saunders Company, 1928.

10. Howell, W. H.: Textbook of Physiology, 10th ed., Philadelphia, W. B. Saunders Company, 1929, p. 978.

11. MacLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, 6th ed., St. Louis, The C. V. Mosby Company, 1930, p. 953.

12. Wright, S.: Applied Physiology, 4th ed., New York, Oxford University Press, 1931, p. 398.

13. Linder, F. E., and Carmichael, H. T.: A Biometrical Study of the Relation Between Oral and Rectal Temperatures in Normal and Schizophrenic Subjects, Human Biology. (To be published.)

14. Hoskins, R. G., and Sleeper, F. H.: Arch. Neurol. and Psychiat., 1933, **30**, 123.

15. Kraepelin, E.: Dementia Praecox, Trans. by R. Mary Barclay, Edinburgh, E. and S. Livingston, 1919.

16. Bleuler, E.: Textbook of Psychiatry, New York, The Macmillan Company, 1930, p. 59.

17. Singer, H. D.: Mental Disorders, Nelson's Loose Leaf Living Medicine, New York, Thomas Nelson and Sons, 1927, **6**, 707.
18. Langfeldt, G.: The Endocrine Glands and Autonomic Systems in Dementia Præcox, Bergen, J. W. Eides Boktrykkeri A/S, 1926, p. 18.
19. Williams, S. W. D.: Med. Times and Gaz., 1867, **2**, 224.
20. Zenker, W.: Allg. Ztschr. f. Psychiat., 1876–1877, **33**, 1; Abstr. Schmidt's Jahrb., 1877, **173**, 180.
21. Snell, O.: Ibid., 1898, **55**, 305.
22. Lyon, D. M., and Wallace, H. L.: Mean Temperature in Non-febrile Hospital Patients, Brit. Med. J., 1932, **1**, 980.
23. Whiting, M. H.: Biometrika, 1915, **11**, 1.
24. Paton, J. H. P.: Brit. Med. J., 1932, **2**, 142.
25. Rautmann, H.: Ztschr. f. Konstitutionslehre, 1928, **13**, 588.

INSULIN THERAPY IN TUBERCULOSIS.

By Andrew L. Banyai, M.D.,

CLINICAL DIRECTOR, MUIRDALE SANATORIUM, WAUWATOSA, WIS.; CLINICAL INSTRUCTOR IN MEDICINE, SCHOOL OF MEDICINE, MARQUETTE UNIVERSITY, MILWAUKEE, WIS.; PRECEPTOR IN TUBERCULOSIS, SCHOOL OF MEDICINE, UNIVERSITY OF WISCONSIN, MADISON, WIS.,

AND

George H. Jurgens, M.D.,

SENIOR RESIDENT PHYSICIAN, MUIRDALE SANATORIUM, WAUWATOSA, WIS.

(From Muirdale Sanatorium, Wauwatosa, Wis.)

The problem of adequate nutrition is of utmost importance in pulmonary tuberculosis. A great many tuberculous patients are of normal weight, or their weight can be restored to normal by rest and exposure to fresh air, or in addition to these by local interventions, such as artificial pneumothorax, phrenic nerve block, etc. However, there is a definite group of patients who, in spite of appropriate therapeutic measures, stay undernourished. Mostly moderately and far-advanced cases belong to this class. In this group, attempts to correct the lack of appetite, to increase the food intake and to improve the nutritional status, often fail even when the well-known medicines, such as dilute hydrochloric acid and stomachics, are used; or when the diet is corrected and regulated, and constipation, if present, is eliminated.

We have used insulin for such patients having an active, moderately (24 cases) or far-advanced pulmonary tuberculosis (19 cases). This was based on the favorable results seen by Marriotte[1] and Barbour[2] in undernourished infants (1924), and by Falta[3] in adults (1925) in a great variety of diseases, including tuberculosis. Investigations on the carbohydrate metabolism in the tuberculous were also highly suggestive in this regard. Rabuchin[4] found in tuberculous animals a hypoglycemia during the first 2 weeks that became worse, returned to normal, or developed into hyperglycemia during the latter course of the disease. Necropsy revealed that there is a

tendency to a productive proliferative process in the pancreas, with atrophy and necrosis of the lobuli and contraction and sclerosis of the islands of Langerhans, resulting in hypofunction of the pancreas. Furthermore, the liver showed a very low glycogen content, the latter being the result of the increased metabolism caused by absorption of toxins or, as has been shown by Lawrence,[5] by a shortage of insulin. Rabuchin[4] also observed that following the administration of glucose orally or intravenously in tuberculous patients, there was a rapid, sharp and higher than normal rise in the blood sugar, followed by a slower return to its original level than seen in normal persons.

Several of the patients included in our group were strict bed patients. Only 8 were afebrile, 24 had temperature below 37.5 C (99.5 F). The temperature was between 37.5 and 38.5 C (101.3 F) in 8, and over 38.5 C in 3. Complications in these patients were: chronic interstitial nephritis, 1; renal tuberculosis, 1; renal and intestinal tuberculosis, 1; intestinal tuberculosis, 3; rectal fistula, 1; rectal fistula and Pott's disease, 1; tuberculous laryngitis, 4; tuberculous laryngitis and corneal ulcer, 1; pregnancy, 1; allergic asthma, 1; and ichthyosis, 1.

It may be thought that such patients might have represented, *a priori*, a poor prognosis and only slight opportunity, if any, to accomplish the desired effect. Still, such a selection seemed to be justified: 1, because tuberculous patients in the earlier or quiescent stages are, as a rule, in no need of forced nutrition; 2, because it was expected that, by inducing better ingestion, absorption and assimilation of food, one might be able to improve the condition of the body tissues and thus to increase the defense mechanism of the body in these stationary and often apparently intractable cases. It is a matter of conjecture that perhaps the effect of insulin on fat metabolism, as manifested by increased deposition of fats in experimental animals and in diabetics taking insulin, might favorably influence the course of tuberculosis. Animals kept on a high-fat diet showed better resistance against tuberculosis than those kept on ordinary diet; 3, because insulin may establish an increased endogenous production of insulin even after injections having been discontinued. Such an explanation was given by Metz[6] for the maintenance of improved appetite and continued gain in weight after the termination of insulin treatment.

Our experience taught us that it is safer to begin the treatment with 5 units 3 times a day, ½ hr. before meals, and increase it to 3 times 10 units or more daily, if necessary. This precaution is advisable because of the possibility of administering insulin to patients with hypoglycemia and thus causing a disagreeable reaction. Rabuchin[4] found that the blood sugar was below 80 mg. per cent in 12.3% in pulmonary tuberculosis cases in Turban's first and second stage and in 22.4% in Turban's third stage. Six per cent of the cir-

rhotic, 25.5% of the productive nodular, and 28.8% of the exudative cases showed the same low blood sugar. The maximum amount of insulin given on one day was 3 times 15 units in this series. Only one patient went into a semicoma while taking 10 units 3 times a day. This patient had fever and a high pulse rate. Her appetite was not influenced by insulin and her food intake was not satisfactory. The reaction reached its peak in 3½ hr. following the injection, during the afternoon "rest hours." It was promptly checked by intravenous glucose injection and by giving several glassfuls of orange juice with sugar. This occurrence probably could have been prevented by closer watch over the patient, and indicates the necessity of constant supervision of insulin treated patients. One patient developed abdominal pain, nausea and vomiting after each injection of 10 units of insulin, a condition not unlike that recently described by Williams[7] as gastro-intestinal allergy due to insulin. In 1 case the insulin was discontinued because of headaches, dizziness and extreme weakness following injections, although the appetite showed marked improvement. Almost one-half of our patients reported slight weakness, tremor and shakiness prior to the development of hunger. It is a good policy to tell the patients about the probability of such mild hypoglycemic reaction, before the treatment is begun.

Allergic Skin Reaction. This was seen in 5 cases. Two of these developed generalized urticaria with intense itching; one on the 23d day, for 5 days; the other on the 10th day of her second course. Both of these patients were given 10 units 3 times a day. The 3d patient reported that a swelling the size of a large walnut, with slight tenderness, itching and redness, appeared at the site of each injection of 10 units. This reaction was first noticed during the second week of treatment and none was seen during the last 2 weeks of the 10 weeks' insulin treatment. His appetite showed great improvement after the treatment was stopped. In the 4th case of insulin hypersensitiveness, the appearance of a hard swelling with a superficial erythema at the site of injection began on the 8th day of the course during which 5 units were given 3 times a day. These reactions appeared in about 6 hr. and lasted for 2 days. No gain in weight was noted in this case, although the appetite became better and the amount of food ingested was greater than before. The 5th patient developed a slightly reddened, itching, hard swelling the size of a small walnut following injections of 10 units of insulin, which gradually disappeared in 2 days during the first 2 weeks of the course. This patient had excellent appetite in spite of these reactions. Both of these types of allergic reactions were analyzed by Tuft[8] in detail. Allan and Scherer[9] studied 100 cases in which allergic manifestations occurred during insulin treatment in diabetics. They found that reactions occur from insulin obtained from every source, although there were differences in the number of

reactions from different lots of insulin. We have not observed insulin hypersensitiveness in an about equal number of diabetics who also had pulmonary tuberculosis, prior to the use of insulin in non-diabetics. Nor have we seen allergic reactions in diabetics who were given insulin from the same lot used for our non-diabetic patients. It must be assumed that a possible profound change in the allergic status of patients with diabetes and tuberculosis is responsible for the absence of allergic reactions in the tuberculous diabetic.

Spontaneous desensitization occurred in 2 of our cases who had marked local reactions. In the urticarial cases the insulin was discontinued immediately. Allan and Scherer[9] obtained relief from irritation by using insulin from a different source. Their efforts to bring about desensitization deliberately were not very satisfactory.

The diet of our patients consisted of the regular meals served to sanatorium patients, supplemented by milk, crackers and bread in the forenoon, afternoon and before retiring, according to their appetite.

Therapeutic Results. Of the 24 moderately advanced cases, 11 developed a marked, 7 a moderate and 1 a slight improvement of the appetite. No change was noted in 4, and the appetite became worse in 1. Of the 19 far-advanced cases the appetite greatly increased in 3, moderately in 4 and slightly in 4; it remained unchanged in 6, and became worse in 2. In those benefited by the treatment, the improvement was noticeable, usually, on the first day or during the next 2 to 3 days. The appetite remained good throughout the course of treatment in the great majority of cases. Lack of increase of appetite during, and appreciable increase after insulin treatment were seen in 2 patients who were treated for 2 and 10 weeks, respectively. The appetite became ravenous in some patients. The hunger appeared about ½ hr. after the injection, with the exception of 1 patient whose insulin had to be given 15 min. before meals because of his early hunger reaction. Hunger during the forenoon, afternoon and 2 to 3 hr. after supper was reported by several patients. The appetite increased after the discontinuance of insulin in 5 moderately and 1 far-advanced case, remained improved but stationary in 11 and 9 cases in these respective groups, and diminished in 4 moderately and 8 far-advanced cases.

Gain in weight was recorded in 13 (54.1%) of the moderately advanced and in 9 (47.3%) of the far-advanced cases. This was maintained by the majority (69%) in the moderately advanced but only in 44% in the far-advanced group during the next 2 months of observation. Additional gain was recorded in 2 of the first group. Gain in weight was lacking during, but noted after the discontinuance of insulin in 2 patients of the first and in 1 of the second group. The gain in weight averaged 1 pound per week in several instances. The maximum average weekly increase was 2.9 pounds. The end-results showed as high as 11% gain in weight in 1 case, and between

5 and 10% in several patients. The largest individual gain was 13 pounds during the treatment.

The longest continuous treatment lasted for 17 weeks. One patient was given 2 courses which together lasted for 20 weeks. The length of treatment in the remaining cases was from 2 to 14 weeks. Attempted treatment or treatment which lasted less than 2 weeks was given in 1 case of gastro-intestinal insulin allergy, 1 case which developed semicoma, 1 with severe nervous reaction, and 3 with extreme weakness following injections. Of the 4 patients who had 2 courses, 1 developed a severe generalized allergic reaction, in 1 the response was not satisfactory, and improved appetite was noted in 2.

A transient elevation of the temperature which could have been attributed to insulin occurred in 2 instances. However, a close study of the temperature charts of these patients revealed a similar "auto-tuberculin" reaction prior to the use of insulin. Frank hemorrhage was not observed during the treatment. One patient who had it prior to the treatment had not developed any tendency to hemorrhage while on insulin. Streaked sputum was seen in 3 patients who had similar occurrence before. It cleared up by routine measures in a few days. We have not observed focal reaction in our patients which could have been due to insulin. On the contrary, improvement in the pulmonary process was found in 6 patients during or following the insulin treatment. Although we feel that this might have been a coincidence, it is reasonable to suppose that one might be able to aid resistance, defense, and repair by improving the nutritional condition of the tissues.

We found the following points of great practical importance: 1, The dosage should be adapted to the individual case; 2, severe reactions must be avoided by proper instruction of the patients as well as the nurses, with particular attention to the "rest hours" when the sanatorium patients, as a rule, are without direct supervision and when a coma may set in insidiously. Each patient must have an easily accessible supply of food of high carbohydrate content; 3, the tray of strictly bed patients must be checked after it is returned and, if it is found that insufficient amount of food was ingested, the patient should be given enough carbohydrates; 4, insulin must be discontinued in case of an urticarial reaction, while it may be continued in patients who react with an indurated swelling at the site of injection because these patients, usually, become desensitized spontaneously; 5, the injections should be discontinued if there is no favorable response in 2 weeks.

Summary. Observations on the effect of insulin in 43 non-diabetic patients with active, moderately and far advanced pulmonary tuberculosis are presented. Insulin therapy was found to be of value in that it improved the appetite in 19 (79.1%) of the 24

moderately advanced cases and in 11 (57.8%) of the 19 far-advanced cases. It increased the weight in 13 (54.1%) of the moderately advanced and in 9 (47.3%) of the far-advanced cases.

REFERENCES.

1. Marriotte, W. McK.: J. Am. Med. Assn., 1924, **83**, 500.
2. Barbour, O.: Arch. Pediat., 1924, **41**, 707.
3. Falta, W.: Wien. klin. Wchnschr., 1925, **38**, 757.
4. Rabuchin, L. E., quoted by Banyai, A. L.: Am. Rev. Tuberc., 1931, **24**, 650.
5. Lawrence, R. D., quoted by Banyai, A. L.: Ibid., 1931, **24**, 650.
6. Metz, R. D.: J. Am. Med. Assn., 1931, **96**, 1456.
7. Williams, R. J.: Ibid., 1933, **100**, 658.
8. Tuft, L.: Am. J. Med. Sci., 1928, **176**, 707.
9. Allan, F. N., and Scherer, L. R.: Ibid., 1933, **185**, 815.

THE CINCHOPHEN OXIDATION TEST OF LIVER FUNCTION IN PULMONARY TUBERCULOSIS.

By John B. O'Connor, B.A.,

Herbert Young, M.D.,

John Steidl, M.D.,
FIRST ASSISTANT RESIDENT PHYSICIAN,

AND

Fred H. Heise, M.D.,
MEDICAL DIRECTOR, TRUDEAU SANATORIUM, TRUDEAU, N. Y.

Liver damage varying in type and extent has been frequently noted at the autopsy table in patients dying of pulmonary tuberculosis. Two of us have shown[1] that if a variety of the currently accepted tests of liver function are used, this liver damage may be demonstrated during life in a high percentage of very ill patients with advanced disease. During the course of these studies we found the cinchophen oxidation test of hepatic function (Lichtman) to be the most sensitive; at least it gave the largest number of positive results among the liver function tests used by us.

Having demonstrated the frequency of liver damage in advanced disease, the question arose as to how frequently disturbance of liver function occurred in other types of our patients.

The incidence of liver function disturbance as demonstrated by the cinchophen oxidation test was determined in 115 consecutive, unselected patients admitted to the Trudeau Sanatorium. An attempt was also made to correlate liver function disturbance with the activity, extent and character of the pulmonary tuberculosis,

studying the symptoms of the patient, the Roentgen ray film, the leukocytic reaction according to Medlar's count and the blood sedimentation rate.

Briefly, the cinchophen oxidation test consists in feeding the patient 0.45 gm. of cinchophen and determining colorimetrically the output of oxycinchophen in the urine. According to Lichtman[2]* 100 mg. or less of oxycinchophen are excreted in the urine of normal subjects. When an amount in excess of 100 mg. is found in the urine, liver insufficiency is considered to be present, higher figures indicating greater insufficiency. We have had almost no experience with this test other than with tuberculous patients, and therefore accept the status of the test as it appears in the literature.

Incidence. The incidence of hepatic insufficiency in this group of cases was very high. Among 24 cases classified minimal-A (American Sanatorium Association), 22 excreted more than 100 mg. of oxycinchophen, the average being 211 mg. Among 72 patients classified moderately advanced-A, 68 excreted more than 100 mg., the average being 194 mg. Ten patients classified far-advanced-A, all excreted more than 100 mg. Of 3 patients classified far-advanced-B, 2 excreted more, and 1 less than 100 mg. The far-advanced patients excreted an average of 207 mg. Thus 91% of minimal, 94% of moderately advanced and 92% of far-advanced cases showed evidence of hepatic insufficiency as determined by the cinchophen test.

Relation of the Cinchophen Oxidation Test to the Activity of the Disease. An attempt was made to correlate the degree of insufficiency, as indicated by the amount of oxycinchophen excreted, with other factors which have been found useful in the evaluation of activity of pulmonary tuberculosis.

Clinical Symptoms. Patients are regarded as symptomatically active or inactive largely on the basis of pulse and temperature, although when these are normal a patient is sometimes regarded as symptomatically active when he has marked fatigue or other symptoms. The symptomatically active patients in this series excreted an average of 210 mg. of oxycinchophen; those symptomatically inactive an average of 194 mg.

Roentgen Film. The activity of the disease was estimated on the basis of the first Roentgen ray film taken on admission. The patients whose films were interpreted as active excreted an average of 195 mg. Those whose films were interpreted as inactive excreted an average of 205 mg.

Patients whose disease was regarded as exudative on the basis of the Roentgen ray film excreted an average of 200 mg., while the excretion of the proliferative group averaged 194 mg. While the exudative group excreted a somewhat larger amount of oxycincho-

* We are indebted to Dr. Lichtman for aid, suggestions, and friendly criticism both by correspondence and on the occasions of his visits to our laboratory.

phen, there were striking individual examples of very low excretion with exudative disease, and very high excretion with proliferative disease.

Blood Sedimentation Rate. The sedimentation rate (Cutler method) was regarded as active when above 8 mm. in men and above 10 mm. in women. Patients with an active sedimentation rate excreted an average of 205 mg.; those with an inactive sedimentation rate an average of 193 mg.

Leukocyte Count. Patients with a normal count excreted an average of 193 mg., those with a resistant count 197 mg., and those with a hyperplastic count 115 mg. As only 3 patients fell into the last group, this figure has little significance. Patients with a septic count excreted an average of 202 mg. of oxycinchophen.

It is apparent that there is little variation in the amount of oxycinchophen excreted by individuals in the active and inactive groups, judged by any of these criteria. Furthermore, a few cases were also noted in which there was marked activity of the disease and a normal excretion of oxycinchophen and *vice versa.*

Comment. If the cinchophen oxidation test is to be relied on, it is apparent that hepatic insufficiency occurs in a very high percentage of all types of pulmonary tuberculosis. In an effort to determine the duration of this insufficiency and its relationship to the clinical course of the diseases, the test is now being repeated periodically on a group of patients.

An attempt to correlate the activity of the pulmonary tuberculosis with the excretion of oxycinchophen has been disappointing and it is apparent that this test is not equal in practical clinical value to other accepted criteria of activity. The results suggest that, even though the foci of pulmonary tuberculosis may become clinically quiescent, secondary functional or organic hepatic changes may persist indefinitely in many patients. We hope to acquire more definite information on this point during studies which are now in progress.

There may be unknown factors involved in tuberculosis that cause the abnormal oxidation. Apparently mechanical factors, such as the volume of diseased lung or the presence of pneumothorax, have no important influence on the oxidation of cinchophen.

Conclusions. Hepatic insufficiency, as indicated by the cinchophen oxidation test of hepatic cell function, occurred in more than 90% of a group of consecutive unselected patients with pulmonary tuberculosis admitted to Trudeau Sanatorium.

REFERENCES.

1. Steidl, J. H., and Heise, F. H.: Am. J. Med. Sci., 1933, **186**, 631.
2. Lichtman, S. S.: Arch. Int. Med., 1931, **48**, 98.

GAUCHER'S DISEASE.

REPORT OF A CASE WITH PRESENTATION OF A TABLE DIFFERENTIATING THE LIPOID DISTURBANCES.

BY AARON CAPPER, M.D.,
ASSOCIATE PEDIATRIST,

HERMAN EPSTEIN, M.D.,
ASSISTANT PEDIATRIST,

AND

ROBERT A. SCHLESS, M.D.,
CHIEF PEDIATRIST, JEWISH HOSPITAL, PHILADELPHIA, PA.

(From the Pediatric Service of Dr. Robert A. Schless, Jewish Hospital.)

SEVERAL reasons prompt us to report the following case of Gaucher's disease. 1, The number of authentic cases reported is still sufficiently small to warrant placing an additional one on record; 2, an error in the diagnosis made during the earlier admission of this girl makes it important to stress that point in order to prevent its repetition; 3, this patient's condition since she was subjected to splenectomy is instructive; 4, microincineration of sections of the spleen has not been done heretofore in this disease; 5, the results of the chemical examination of the spleen for kerasin are worth noting.

Gaucher's disease is generally understood not to be hereditary in character, and thus far Anderson's[1] is the only hereditary case that has been reported. It is now regarded as a congenital, primary and familial constitutional disease in which the lipoid kerasin, belonging to the cerebrosids, is stored in foam cells, measuring usually 20 to 40, and occasionally up to 100 microns in diameter, the so-called Gaucher cells; these, according to Pick,[3] are derivatives of the reticulum cells (especially so in the spleen) and they invade the spleen, liver, lymph nodes, and bone marrow and, if the disease occurs in infancy, also the thymus, tonsils, lymph tissue of intestines, lungs, and even the cerebral cortex. The substance kerasin, the chemical formula of which was given by Rosenheim[4] as $C_{47}H_{91}NO_8 \cdot H_2O$, is a compound having properties very similar to phrenosin, and accompanies phrenosin in tissues of the nervous system, both constituting a cerebrosid or glycolipin. On acid hydrolysis, kerasin yields lingoceric acid ($C_{24}H_{48}O_2$), sphingosin and *d*-galactose.

Gaucher's disease shows a particular predilection for individuals of the Jewish race. It is more common in females, occurring in the proportion of about 2 to 1. It is characterized by a slow and insidious onset, a gradual enlargement of the spleen, followed later by an increase in the size of the liver. The patient develops a hypochromic anemia, thrombopenia, and a leukopenia, due to infiltration of the bone marrow by foam cells. Hemolysis is an additional

FIG. 1.—Note the Erlenmeyer-flask appearance of lower ends of both femora. Irregularity of cortex probably due to previous operations. Areas of osteolysis are also characteristic of Gaucher's disease.

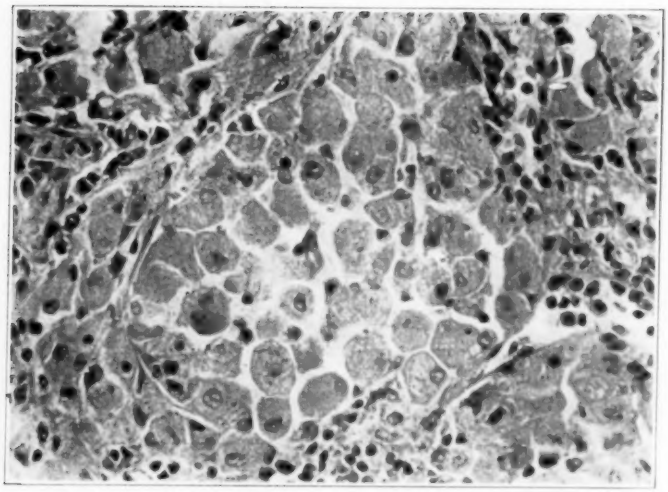


FIG. 2.—High power: Section of spleen shows nests of large Gaucher cells possessing eccentric nuclei and considerable clear protoplasm. Most of the cells possess one nucleus; a few are multinucleated. Cells are fairly uniform in size. They are surrounded by connective tissue.

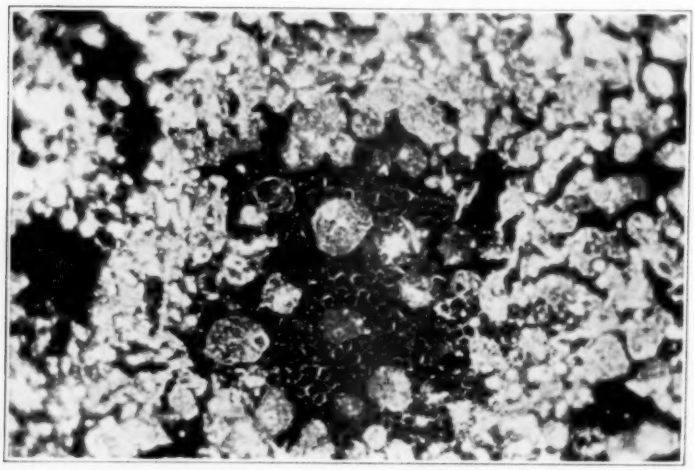


FIG. 3.—Section of splenic tissue after microincineration. Note the normal amount of inorganic material in the cytoplasm of the Gaucher cells and the high concentration of ash in the peripheral zone of the nuclei.

factor in the production of anemia. Enzer,[2] in the discussion of Anderson's case, says that leukopenia is not necessarily characteristic and essential for the diagnosis; he saw 3 cases of Gaucher's disease which showed a rather marked leukocytosis. About ½ of the patients develop pigmentation of the exposed skin, which depends upon the hemosiderin liberated as a result of increased blood destruction. A prominent and supposedly characteristic finding mentioned by many authors is the yellow-wedge-shaped pinguecula of the sclera or conjunctiva. It appears now that this sign is not present as frequently as had been thought, occurring in only 14 out of 89 cases summarized by Hoffman and Makler.[5] It is even less common in children; present in only 10% of cases. The large spleen may be found only accidentally in the course of a general examination, as in our case. The patient may complain of a variety of symptoms related to the osseous system. Some may only have vague pains in the limbs or joints, giving rise to the diagnosis of "growing pains," or, as in the case of Milch and Pomeranz,[6] to "rheumatism." In others the pain may be acute and violent, and lead to the mistaken diagnosis of acute osteomyelitis, as was true in our case, in an additional one reported by Milch and Pomeranz,[6] and in 1 of the 2 cases reported by Potter and McCrae.[7] This tenderness or pain in the bones is probably due to the increased subcortical pressure caused by the infiltrating masses of Gaucher cells. In some patients the only complaint is that of pain or tenderness in the region of the spleen, or the patient's attention is drawn to the enlarged abdomen. When the blood platelets fall to a sufficiently low number there frequently ensue blood extravasations into the skin or mucous membranes, although there is no direct proportion between the number of platelets and the bleeding phenomena. In our patient, purpuric spots did not appear on the face, forearms, and conjunctivæ until the platelets dropped to 40,000; and yet, on a later occasion, when they were 29,400, she had no hemorrhages.

Gaucher's disease does not produce cerebral symptoms except in infancy, when various neurologic findings may predominate, thus simulating Niemann-Pick's disease. Oberling and Woringer[8] refer to the syndrome of opisthotonos, spasticity, strabismus, and nuchal rigidity in infancy as "progressive decortication." Moncrieff[9] reported this syndrome in a 10-week-old infant. These cerebral manifestations are probably due to the infiltration of foam cells in the cerebral cortex and other parts of the brain.

We offer the following table of the known diseases of lipoid metabolism, to delineate the similarities and contrasts of these disturbances related to Gaucher's disease.

Case History.—M. K., Jewish girl, aged 10 years, was first admitted on May 1, 1929, at the age of 6½ years. Her past medical history is negative. Her father, mother, 3 brothers and 1 sister were examined for Gaucher's disease and found to be negative. The chief complaint on admission, was pain and swelling of the right thigh just above the knee of several days'

TABLE 1.—XANTHOMATOSES OR LIPOIDOSES—DISEASES DUE TO DISTURBANCES IN LIPOID METABOLISM.
(Rowland.) (Pick.)

Name.	Type of lipoid	Blood findings.	Eye grounds.	Spleen, liver glands.	Age.	Bones.	Pathognomonic features.	Skin.	Treatment.	Remarks.
A. Gaucher's disease (90–100 cases)	Cerebrosid (kerasin-A sphingo-galactid)	1. Hypochromic anemia 2. Leukopenia 3. Thrombopenia 4. Later, hemorrhagic diathesis	Negative	Spleen markedly enlarged Liver enlarged Slight or no lymph-adenopathy	Infancy to adult life	Mottling and rarefaction with cortical thinning, flasklike appearance ends of femora	1. X-ray appearance of long bones, especially femora 2. Splenic puncture 3. Bone-marrow examination	Subicteric pigmentation of exposed parts in 45%. Yellow thickened pingueculæ in eyes in 15%	Splenectomy (fatal in 20%) or radiation (both palliative)	Common in Jews.
B. Niemann-Pick's disease or lipoid histiocytosis (Bloom)	Phosphatids	1. Moderate secondary anemia 2. Slight leukocytosis 3. Vacuolization of non-granulated cells 4. Excess of lipoids in blood	Cherry-red spot in macula lutea *occasionally* found	Spleen and liver very large Moderate lymphadenopathy	Infancy	Any bones or organs may be invaded by the foam cells	Splenic puncture	Brownish-yellow discoloration	No treatment, all fatal	Mental retardation may be present resembling Tay-Sachs' disease. Most common in Jews.
C. Hand-Schüller-Christian disease (45–50 cases)	Cholesterol and its esters	There may be a hypercholesteremia	Negative	Not enlarged	Any age	Membranous bones involved	1. Defects in membranous bones 2. Diabetes insipidus 3. Exophthalmos 4. Gingivitis and stomatitis 5. Adiposogenital dystrophy	Negative	X-ray treatment of involved area causes prompt local healing but does not stop the progress of the disease.	
D. Tay-Sachs' disease or amaurotic familial idiocy	A prelipoid	Negative	Cherry-red spot in macula lutea *usually* found	Usually negative	Infancy	Not involved	1. Eye grounds 2. Mental retardation 3. Hyperacousis	Negative	All fatal	Brain shows prelipoid deposits in granular layer and about dendrites of the Purkinje cells Most common in Jews.
E. Xanthomatoses of skin, etc.	Cholesterol and its esters	Negative	Negative	Negative	Any age	Any bones may be involved	.....	Xanthomatoses of any part of skin	Excision, if tumorous.	

duration. Her temperature was normal and rose to 100.8° 2 days following operation, when it again dropped to normal and remained so until her discharge. The right femur was trephined, free "pus" obtained, a drain inserted and Dakin solution dressings applied. The wound healed in 3 weeks. *It should be noted at this time that the smears and culture of the "pus" obtained were negative.* Her next admission was over a year later, on May 17, 1930, because of pain in the center of the left thigh, which began 24 hr. previously. The temperature was 100.2°. The Roentgen ray of the left femur showed a slight irregularity of its shaft, just below the middle third, with some decalcification just above the knee joint. A diagnosis of acute osteomyelitis of the left thigh was made and the femur was trephined and drained. *The exudate at operation was gummatous in character, and a smear and culture were negative.* Eight days after operation, when her wound was still draining and her temperature was elevated to 100.2°, her white cell count was 6000, the first report of a leukopenia. She was discharged as cured on June 6, 1930.

Her 3d admission took place on July 8, 1930, 1 month later, because of redness, swelling, and tenderness of the left femur over the scar of the previous operation. *Her temperature was 100° F., and the white cell count was only 6000, again a leukopenia.* The medullary cavity of the left thigh was curetted, and a sequestrum removed. She was given a blood transfusion of 125 cc. On August 12, 1930, it was discovered by one of us that the spleen was very much enlarged, reaching down to the pelvic brim. The liver was increased in size, though not as much as the spleen. Although this was the first time that the enlarged spleen and liver were noted, it is probable that they had been so for some time, but were overlooked on account of the concentrated attention on the lower extremities. The nurses remarked that the patient's abdomen had been unduly prominent for some time. The mother later stated that the patient always had a definitely prominent abdomen. At this time on account of the history of osteomyelitis, a peculiar waxy pale complexion, a hemoglobin of 31%, continuous albuminuria and a complicating diarrhea together with the splenomegaly, a provisional diagnosis of amyloidosis was made. On August 14, 1930, the roentgenologic examination showed small areas of decalcification with a *slight widening of the diaphysis near the knee-joint,* which were interpreted as being the result of a chronic osteomyelitis. The right humerus, lumbar vertebræ and sacroiliacs appeared normal. Her 4th admission on August 13, 1931, was for the purpose of draining a superficial abscess of the left thigh.

Her fifth admission on October 3, 1931, was for the purpose of determining the cause of the splenomegaly and anemia. Her general physical condition was unchanged. She was pale and there was no definite pigmentation except that her face showed elements of pigment, reminding one of the facies of a pregnant woman, the so-called "chloasma uterinum." The conjunctivæ showed no pigmentation. The Mantoux test was negative. The two significant findings at this time were the leukopenia, 6500 white cells on October 5, 1931, and the thrombopenia, 50,000 platelets on October 6, and 55,000 3 days later. This was the first time that a thrombopenia was found; Gaucher's disease was suspected and a splenic puncture advised. The parents refused permission for the procedure and the patient was discharged 17 days after admission. Her 6th admission on May 27, 1932, was for the purpose of curetting a sinus in the left leg.

The 7th time she came in on January 7, 1933, because the spleen was slowly increasing in size. The upper border of the liver was found by percussion in the 4th interspace, while the lower border was 1½ inches below the costal margin. The upper border of the spleen was at the 5th rib in the axillary line, the lower border was 2 inches below the crest of the ilium, and the right border reached to the midline. It was not tender on palpation.

TABLE 2.—BLOOD STUDIES IN A CASE OF GAUCHER'S DISEASE (4½ YEARS).

Date.	Hemoglobin, per cent.	Red cells in millions.	White cells in thousands.	Neutrophils, per cent.	Lymphocytes per cent.	Large mononuclears, per cent.	Transitionals, per cent.	Eosinophils, per cent.	Platelets in thousands.	Reticulocytes, per cent.	Special.
May 1, 1929	71	4.0	15.5	69	31						
May 17, 1930	64	4.0	9.2	65	35						
May 25, 1930	..	....	6.0								
July 9, 1930	60	4.65	6.0	52	47	..	1	..	.....	...	Slight anisocytosis.
July 25, 1930	31	2.1	7.4	57	41	1	1	..	.....	...	Some aniso- and poikilocytosis.
July 26, 1930	30	2.0	7.1	58	42	..	..	..	.....	...	Marked anisocytosis and achromasia.
July 31, 1930	40	2.55	5.4	75	25	..	..	..	.....	...	1 Türck cell; 2 days after transfusion.
Aug. 2, 1930	42	2.6	13.3	56	44	..	..	..	.....	...	Many poikilocytes.
Aug. 12, 1930	44	2.5	7.1	50	49	..	1				
Aug. 13, 1930	42	2.6	6.6	59	41						
Aug. 14, 1930	50	3.3	7.0	50	50	..	..	..	330	0.1	Marked anisocytosis.
Aug. 15, 1930	50	3.0	5.2	48	47	2	3	..	.....	...	Marked anisocytosis.
Aug. 16, 1930	53	3.0	4.8	42	48	..	..	..	.....	...	Some anisocytosis.
Aug. 27, 1930	67	4.05	5.3	59	40	..	1	..	.....	...	Slight anisocytosis.
Sept. 5, 1930	67	3.9	7.0	54	44	..	2				
Sept. 22, 1930	70	4.45	7.2	65	35						
Oct. 28, 1930	57	3.85	6.8	60	40						
Oct. 5, 1931	56	3.35	6.5	43	55	..	2	..	50	0.4	B.T. 5 min., C.T. 5½ min.
Oct. 9, 1931	..	.....	....	..	..	..	..	..	55	...	Hemol. begins at 0.44, hemol. complete at 0.32.
Jan. 10, 1933	81	4.6	7.0	52	44	2	..	2	65	1.0	1 Türck cell.
Jan. 23, 1933	80	4.8	5.0	40	60	..	..	..	40	...	B.T. 4 min., C.T. 4½ min. Clot retraction delayed.
Jan. 27, 1933	..	....	....	..	..	..	..	..	45	...	B.T. 5 min., C.T. 2½ min.
Jan. 30, 1933	..	....	....	..	..	..	..	..	65	...	Hemol. begins at 0.44, hemol. complete at 0.32.
Feb. 7, 1933	77	4.3	5.0	44	56	..	..	..	30		
Feb. 11, 1933	76	4.2	5.0	44	56	..	..	..	29	...	Day of operation.
AFTER SPLENECTOMY AND TRANSFUSION OF 225 CC. OF BLOOD.											
Feb. 12, 1933	..	....	....	..	..	..	..	..	177		
Feb. 13, 1933	85	4.9	16.0	82	12	5	1	..	1.238	...	C.T. 2½ min.
Feb. 15, 1933	87	5.0	14.1	73	18	7	..	2	900		
Feb. 16, 1933	..	....	....	..	..	..	..	..	530		
Feb. 18, 1933	..	....	....	..	..	..	..	..	500		
Feb. 21, 1933	..	....	....	..	..	..	..	..	550		
Feb. 23, 1933	90	4.95	10.5	63	29	5	..	3	495		
Feb. 28, 1933	80	4.7	12.0	74	23	..	2	1 basophil	277		
July 25, 1933	83	4.6	14.6	72	27	..	..	1 basophil	200	...	B.T. 3½ min. C.T. 3¾ min.
July 28, 1933	75	4.2	8.2	50	49	1					
Oct. 12, 1933	76	4.05	9.8	53	47	..	..	..	405		

B.T. = Bleeding time. C.T. = Coagulation time.

A uroselectan test showed a first degree hydronephrosis of the left kidney, which was confirmed by the urologist on cystoscopic examination, and was thought to be due to mechanical pressure by the large spleen. On January 24, for the first time, numerous purpuric spots appeared on the face, forearms and conjunctivæ. The tourniquet test was positive. The platelet count fell to 40,000. The next day, purpuric spots appeared on the lower extremities. These gradually cleared even though the platelets subsequently fell to 29,400. The eye grounds were normal. The roentgenologic examination of February 1, by Drs. Leon Solis-Cohen and Samuel Bruck revealed in the femora "a typical Erlenmeyer-flask-like appearance, due to widening of the shafts at their distal portions and a narrowing at the junction of their middle and lower thirds; findings characteristic of Gaucher's disease. The normal flaring observed at the femoral condyles was absent. In support of Gaucher's disease there was also a slight sclerosis of the head of the tibia and the presence of transverse growth lines in the fibula. The other long bones and the vertebral column showed no abnormalities."

She was subjected to splenectomy (Dr. Moses Behrend) on February 11 for several reasons. (1) The large spleen was becoming burdensome. (2) The pressure exerted on the left ureter was apparently causing hydronephrosis. (3) It was felt that the bleeding phenomena and the low platelet count could best be controlled by removal of the spleen. (4) Due to the downhill course of the patient it was decided to operate while she was still in good condition. The large spleen was found to be free from adhesions and was removed without difficulty. A blood transfusion of 225 cc. was given immediately following operation. A fresh smear of splenic tissue was examined by Dr. Edward Steinfield; it was found to contain typical foam cells which were very numerous, occupying most of the tissue. Within 24 hr. after splenectomy, the platelets rose to 177,000 and in another 24 hr. to 1,238,000. On February 28, 3 days before the patient was discharged, the platelets were 277,300 and the white count was 12,000. She made an uneventful recovery and was discharged in good condition.

TABLE 3.—OTHER LABORATORY STUDIES.

Date.	Blood Wassermann.	Blood cholesterol.	Blood chemistry.	Special.
Aug. 14, 1930	Negative			
Aug. 16, 1930	.....	166 mg.	Non-protein nitrogen 25 Serum albumin 3.5 Serum globulin 2.6 Total protein 6.25	*Urine*—Faint trace albumin, sp. gr. 1010–1036, 1–6 W. B. C. per low-power field.
Oct. 6, 1931	.....	134 mg.	Blood sugar 91 Urea 17 Non-protein nitrogen 26 Serum albumin 5.6 Serum globulin 2.0 Total protein 7.6	Icterus index, 5.0. Direct Van den Bergh neg. Indirect Van den Bergh 0.1. Stool negative for occult blood, ova and parasites.
Jan. 30, 1933	P. S. P. First specimen 30% Second specimen 35%	147 mg.	.....	Galactose test: First — 85 cc. Second—205 cc. Third — 20 cc. Fourth—185 cc. Fifth —215 cc. } 1.7 gm.
Feb. 9, 1933	.....	.....	.....	Icterus index 13.8.
July 25, 1933	Type IV blood	142 mg.	Blood sugar 84 Urea 9	*Urine*—Trace of albumin to none, sp. gr. 1008–1036. Double refractive bodies absent. 1–10 W. B. C. per low-power field.

The chemical examination of the spleen revealed 6.02% content of kerasin.

C.T. = Coagulation time.
B.T. = Bleeding time.

On July 23, 1933, she was admitted for the 8th time on account of a superficial abscess of the soft tissues of the left thigh, which was incised and drained. No involvement of the periosteum or the shaft of the bone was noted. The child had grown considerably and improved markedly in health since the splenectomy. She had gained 15 pounds in weight.

Pathologic Report (Dr. Samuel Levine). *Gross Description.* "The spleen weighs 1400 gm. The capsule is thickened, having a morocco-leather appearance. The splenic notches are well preserved. On section, the spleen appears very dense in consistency and fleshy in texture. It is deep red in color. Numerous light-grayish specks are noted; the follicles are not easily made out and the splenic pulp presents throughout a fine reticulum of grayish strands. The vessels were injected with formalin to preserve the vascular architecture."

Histology. "A section of the spleen shows destruction of the greater part of the lymph follicles. The sinusoids are occupied by a large number of Gaucher cells having an alveolar arrangement. The cells lie in close proximity to the red blood cells of the splenic pulp. The cells vary in size and shape. Some are oval, others are compressed and elongated, and still others are circular and polygonal in shape. The majority of the cells have a single nucleus, which is fairly well defined and eccentrically located. The cytoplasm is acidophilic and homogeneous in character. A few of the cells are multi-nucleated. Some of the Gaucher cells contain vacuoles. The staining property of these vacuoles serves to differentiate them from histiocytes. Some of the nuclei contain striations running a parallel course. On transverse section to the longitudinal diameter of the cells, these striations appear as stipples. The spleen is loaded with Gaucher cells which occupy a major portion of the organ."

Microincineration studies of the spleen were carried out for us by Dr. Esmond R. Long[10], in order to determine whether a corresponding accumulation of inorganic material accompanies that of the cerebrosid kerasin. "In general, the Gaucher cells were found to have a high content of ash in the nucleus and a low content in the cytoplasm as illustrated in the accompanying figure. Most investigators who have reported on incineration of tissues have called attention to the nuclear ash. In the study here reported the same peripheral distribution of ash was noted as described by Scott and Horning[11] in the nuclei of tumor cells and by Cowdry[12] in the nuclei of liver cells in yellow fever. The nucleoli conspicuous in the sections stained with hematoxylin and eosin could also be observed in the ashed specimens, although not with regularity.

"There was nothing distinctive in the distribution of the ash in the cytoplasm. Iron salts, which can be recognized by their color in ashed sections, were not obsvered. Degenerated cells, poor in material with staining affinity, were also poor in ash, and the large vacuoles characteristic of these cells in the usual preparations were seen in the corresponding incinerated cells. The appearance of the erythrocytes (accompanying figure) was characteristic. The ash was concentrated at the peripheral border. Presumably this was an artefact caused by the fixation and drying of the specimen. However, the peripheral distribution of ash was as marked as that in the nuclei, and if one is an artefact of fixation, the question is properly raised whether the other is not also. The total ash of a specimen from this case, incinerated in a crucible, was 27% of the dry weight. This may be compared with the figure of 15% of the moist weight, or approximately 6% of the dry weight, commonly given for the normal spleen.[13] The incineration study furnishes the explanation for this decrease in ash per unit of weight. The ash is concentrated in the nuclei, and nuclei are present in much larger numbers per unit of volume or of weight in the normal spleen than in the spleen in

Gaucher's disease, the bulk of which is largely due to the cytoplasm of Gaucher's cells or cerebrosid cells, which is relatively poor in mineral matter."

Chemical Examination. The spleen was examined by Dr. John G. Reinhold and found to contain 6.02% of the dried spleen; this is now considered to be quite distinctive of Gaucher's disease. The figure of 6.02% really represents a minimal amount, for it was obtained after the recrystallizing of the chemical material 2 times. Kerasin may make up as much as 10% of the dried spleen, and in one of Cushing and Stout's[14] cases, the crude cerebrosid made up almost 16% of the alcohol extract. The average amount of kerasin in Gaucher's disease reported by most investigators falls within the percentage content found in our case. Phrenosin was also found to be present.

Comment. There are a number of features in this case that deserve special emphasis and discussion. In the first place the question naturally arises, did this child have osteomyelitis and then develop Gaucher's disease, or were her bone affections due to Gaucher's disease primarily? It will be noted that, except for the white cell counts on May 1 and 17, 1929 (15,500 and 9220), she exhibited a leukopenia on practically all other occasions, in spite of the fact that she was supposedly suffering from an acute infectious and pyogenic process. At no time did she really show a septic or even high temperature. On several occasions she had a normal temperature in the presence of pain and swelling of the thighs; and on none of her admissions on account of "acute osteomyelitis" was she toxic. It will be recalled that at the first two operations on the right and left femora the smears and cultures were negative, a finding not expected in acute osteomyelitis. Furthermore, the surgeon noted that the exudate on her 2d admission was *gummatous* rather than purulent, suggestive of Gaucher material. On her 3d admission (August 14, 1930), the roentgenologist already noted a "slight widening of the diaphysis near the knee-joint," apparently the beginning or first stage of the characteristic "Erlenmeyer-flask-like formation." For the above reasons we believe that this patient did not originally suffer from acute osteomyelitis, but that her symptoms were due to Gaucher's disease. Due to operative intervention, pyogenic organisms were introduced from without, leading to secondary bone infection with its subsequent sequestrum formation. It is interesting to remark that in our case the leukopenia preceded the thrombopenia by 16 months. Also, almost 1½ years elapsed between the first finding of a low platelet count and the appearance of hemorrhagic phenomena. It is also worth noting that hemorrhages did not occur until the platelets fell to 40,000.

Realizing that splenectomy in Gaucher's disease is attended by a 20% mortality, we naturally hesitated to advise operation. Our reluctance was further enhanced by Pick's[2] observation that the bones may become more intensely affected following splenectomy. However, in view of the sudden change in the child's condition, the

slight increase in the size of the spleen, the hemorrhagic phenomena, and the continued decrease in platelets, operative interference was deemed a measure of necessity. The splenectomy brought about a normal blood picture and relieved the child of a burdensome abdominal mass which was beginning to cause harmful pressure on the left ureter. The removal of the spleen also improved the child's general health, as she has gained 15 pounds in the 5½ months subsequent to operation. In order to observe whether any changes had occurred in the long bones since the removal of the spleen, we subjected the patient to another roentgenologic study on October 8, 1933. Dr. Leon Solis-Cohen reported no change in the osseous system since the last films were taken, 8 months previously.

We see therefore, that thus far the splenectomy caused no deleterious effect in the osseous system and that it produced a general physical as well as hematologic improvement in her condition. It is, of course, to be remembered that this is a general metabolic disease in which many organs are involved. It is hardly to be expected that the removal of the spleen should effect a cure. The best that can be hoped is a symptomatic improvement and, by removing a large store of Gaucher cells, perhaps temporarily to arrest the course of the disease.

Summary. 1. A case of Gaucher's disease in a Jewish girl is reported that was originally diagnosed as acute osteomyelitis because of the predominance of bone symptoms.

2. Blood counts over a period of 4.5 years showed that leukopenia preceded thrombopenia by about 16 months, and hemorrhagic phenomena did not occur until the platelet count fell to 40,000.

3. Splenectomy produced a cessation of bleeding and persistently normal platelet and white cell counts. The patient gained in weight and improved generally. Thus far, 8 months since splenectomy, there is no clinical or roentgenologic evidence of progression of the disease.

4. The chemical examination of the spleen showed 6.02% of kerasin.

5. Microincineration studies showed a decrease in ash per unit of weight, the Gaucher cell cytoplasm being relatively poor in mineral matter.

6. A chart is appended illustrating the similarities and contrasts of Gaucher's disease with the other diseases due to disturbances in lipoid metabolism.

REFERENCES.

1. Anderson, J. P.: J. Am. Med. Assn., 1933, **101**, 979.
2. Enzer, N.: Ibid., p. 979.
3. Pick, L.: Am. J. Med. Sci., 1933, **185**, 452.
4. Rosenheim, O.: Biochem. J., 1916, **10**, 142.
5. Hoffman, S. S., and Makler, M. J.: Am. J. Dis. Child., 1929, **38**, 775.
6. Milch, H., and Pomeranz, M.: Ann. Surg., 1929, **89**, 552.
7. Potter, E. B., and McCrae, C. C.: Am. J. Med. Sci., 1933, **185**, 92.

8. Oberling, C., and Woringer, P.: Rev. franç. de pediat., 1927, **3**, 475.
9. Moncrieff, A.: Arch. Dis. Child., 1930, **5**, 265.
10. Long, E. R.: Arch. Path., 1933, **16**, 310.
11. Scott, H. G., and Horning, E. S.: Am. J. Path., 1932, **8**, 329.
12. Cowdry, E. V.: Ibid., 1933, **9**, 149.
13. Long, E. R.: Textbook of Physiologic Chemistry, 2d ed., Philadelphia, P. Blakiston's Son & Co., 1909, p. 14.
14. Cushing, E. M., and Stout, A. P.: Arch. Surg., 1926, **12**, 539.

ARTHRITIS, ANABOLIC NUTRITION AND HEALTH.

A Study of the Nourishment and Health of Joints.

By Francis Lowell Burnett, M.D.,

and

Frank Roberts Ober, M.D.,

Boston, Mass.

(From the Health Class for Arthritis at the Peter Bent Brigham Hospital.)

Arthritis, the Anabolic Processes and Cell Regeneration. A failure of nutrient substances to construct or preserve normal bone and cartilage, *i. e.*, a metabolic disorder, has been often considered as the cause of arthritis. Perhaps the atrophy of bone in one type and the loss of cartilage and growth of osteoid tissue in the other type of the disease found by Nichols and Richardson[1] are chiefly responsible for this point of view; because in their basic study "faulty metabolism" is favored as the etiologic agent. This kind of malnutrition from gastro-intestinal disturbances may cause the lesions; for instance, Minot[2] writes that "little is known concerning the difficulties of absorption and utilization of food products from the digestive tract and regarding what particular food factors may improve gastro-intestinal function. . . . It is probable that significant degrees of such disturbances may arise in arthritis and be overcome by well-chosen diets." Some of these disturbances may be corrected by the diet of Fletcher and Graham;[3] for, with the consequent improvement in haustral action, the improved colonic functions appear to favor the nourishment of the joints. In other treatments for this disease, however, as the doctor generally gives dietary directions or patients themselves correct erroneous ways of eating, health is sometimes restored. The result may easily then be ascribed to a natural remission, the administration of drugs, the use of baths, the manipulations of posture, or the injections of proteins or vaccines, if the beneficial effects of right eating and improved absorption on health are not recognized.

Variations in the consumption of food evidently influence its absorption. For by the correction of certain erroneous ways of

eating and living with better functioning of "the secondary digestive pouch"—the proximal colon—the intestinal contents are finally molded into uniform and firm segments, and thus the absorption is improved.[4] (Fig. 1.) The results of this action, by the formation of the entirely segmented or normal feces, are shown in Fig. 2. Such a molding of the colonic contents produces not only these feces but also the normal intestinal rate.* Together these indices signify the complete digestion and absorption of food. Then, if nutrition is defined as the sum of the processes by which an animal absorbs food, and assimilation is the most important phase of the process,[5] the operation of the proximal colon evidently creates a better kind of tissue construction. Since this process suggests improved assimilation, it has been called "anabolic nutrition."[6] In the application of this kind of nutrition to the treatment of disease, a morbid process causing a deficiency or metabolic disorder appears to be replaced by a vital process restoring a state of health. The effect of this change on a superficial tissue may be seen by a comparison of the psoriatic lesions shown in Fig. 3 with the healthy skin of the same person shown in Fig. 4. Such a regeneration of cells following the establishment of anabolic nutrition has relieved this disease in a sufficient number of patients to indicate that spontaneous remissions are not being dealt with.[7,8] As psoriasis is sometimes associated with and is often followed by arthritis, it is suggested that both diseases may be due to malnutrition from the passage of nutrient substances through the digestive tract instead of into the body. The results of malabsorption in deficiency diseases has been pointed out by Burnett and Howe.[9] Of interest also, in the treatment of arthritis as a deficiency disease, is the regeneration of bone cells to relieve experimental scurvy described by Wolbach and Howe.[10] They write that during the disease "the osteoblasts . . . . assumed the shapes of fibroblasts" . . . . but "the administration of orange juice . . . . was followed promptly by the deposition of bone matrix between the fibroblast-like cells." Finally, the arthritic-like lesions produced in guinea pigs from a scorbutic diet alone, and from this diet and an infection, by Rinehart, Connor, and Mettier,[11] still further confirm the metabolic theory of arthritis.

The Creation of Anabolic Nutrition and the Treatment of the Joints. To remove the cause of the arthritis through anabolic nutrition,

* The intestinal rate is an index of absorption, by which the contribution of one meal to the construction of the body is determined. To make the test, from 25 to 50 cc. of French millet seeds or 100 gr. of charcoal are swallowed immediately after an evening meal, and then the number of hours that elapse from the time the marker was ingested to the time the seeds or charcoal are first and last seen in the dejections is observed. In adults producing segmented feces, 1 and 2 dejections are common daily, yet the marked meal takes about 62 hrs. to appear in, and 134 hrs. to disappear from the feces. This rate is considered normal. (Burnett, F. L.: Am. J. Roentgenol., **10**, 359, 1923.)

FIG. 1.—A roentgenogram of the large intestine after a barium meal, showing outlines of the "digestive pouch" formed by the proximal colon and of the uniform masses of the segmented feces in the distal colon.

FIG. 2.—The entirely segmented or normal human feces with which the normal intestinal rate is correlated. Together these indices signify complete digestion and absorption ("anabolic nutrition").

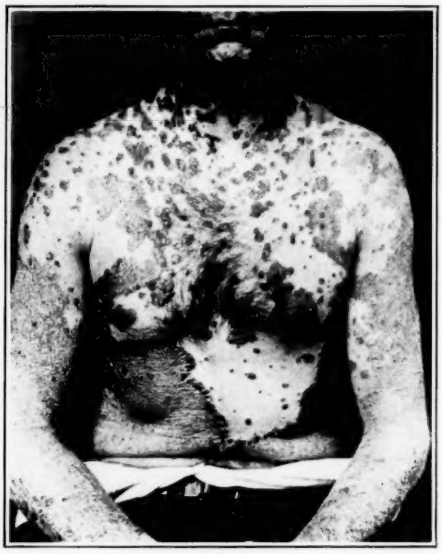


FIG. 3.—The skin of a patient with severe psoriasis.

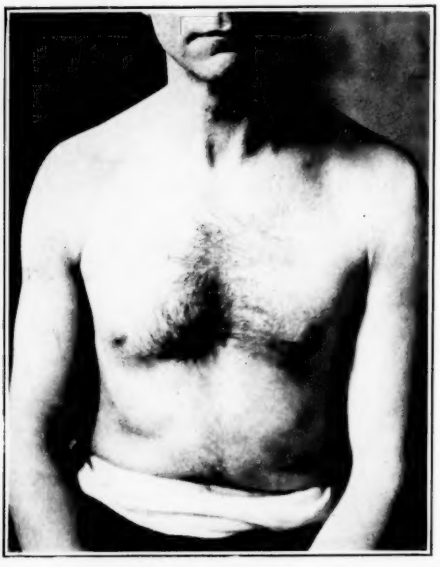


FIG. 4.—The regenerated and healthy skin of the same patient after many months of anabolic nutrition from the correction of erroneous ways of eating.

patients are educated to eat and live in order so to operate the proximal colon that entirely segmented feces and normal intestinal rates are produced. Also, as the digestive fluids are likely to be impotent in these deficient patients, the administration of dilute hydrochloric acid (U. S. P.), gastric enzymes, and enteric-coated pancreatic preparations may be beneficial. Injections of insulin in abnormally lean patients are sometimes helpful. Finally, as it takes months and years of anabolic nutrition to overcome the very deficient condition in these patients, constant encouragement to progress from a state of chronic invalidism and to become more active is very essential. Indeed, this psychologic form of treatment is so important that other forms of therapy, if they do not interfere with the nutrition, may be applied to some patients with profit.

To find out the causes of malabsorption, a detailed inquiry into patients' ways of eating and living is made. Of 30 patients questioned in this way, 19 were found to eat too fast; 17 took laxatives, oil, or enemata regularly; 10 habitually ate cakes, crackers, fruit or candy between meals or before going to bed; 5 ate dinner at noon; 8 ate an excess of breads, cakes, crackers, and other cereal foods; 6 consumed too much protein food; 5 were too fond of fat food; and 19 had an irritable colon and rapid intestinal rate from too much fruit, especially oranges and grapefruit. And most of them ate insufficient vegetables. These erroneous ways of eating caused diarrhea or soft stools; but very obvious signs of indigestion were often revealed by the chemical and microscopic examination of patients' feces. In these tests, poor fat digestion was the most common, starch the next, and protein the least. Some of the stools had an acid reaction to litmus, which was changed to alkalin by treatment. Details of these and other changes in the colonic contents from the correction of erroneous ways of eating are shown in Table 1.

To create anabolic nutrition, patients are taught, from illustrations of the segmented, formed and soft types of the feces and from diagrams and roentgenograms of colonic action, the relation of the fecal specimens and colonic functions to the operations of the nutritive apparatus. They are also given printed outlines which describe the purpose and amplify the directions of the treatment and are shown a form to follow in keeping a record of nutrition. At the top of these records, preliminary directions, such as "eat slowly and only at meal times," and other health measures are written out. Patients then record the food, beverages (except water) and medicines ingested, the time spent at meals, the time and kind of dejections, and determinations of the intestinal rate for a week, and then return with records. Part of a patient's first record of nutrition is often similar to Record 1.

TABLE 1.—THE CHANGE PRODUCED BY ANABOLIC NUTRITION IN THE INTESTINAL RATE, FORM AND REACTION OF THE FECES, AND THE DIGESTION OF A FEW PATIENTS.

Initials of patient.	Dates of examination.	Intestinal rates in hours. *Without laxatives.	Examination of feces.				
			Form.	Reaction to litmus.	Digestion of Protein.	Fat.	Starch.
B. B. A.	9/30/31	13–85	Soft	Acid	Fair	Poor	V. poor
	10/14/31	34–108	Formed	Alkalin	Good	Poor	Poor
L. G. B.	10/24/31	14–60*	Soft	Alkalin	Good	Poor	V. poor
	12/15/31	37–108	Formed	Alkalin	Good	Fair	Fair
M. B. C.	3/19/30	14–108*	Soft	Acid	Fair	Poor	Fair
	12/14/30	63–134	Normal	Neutral	Good	Fair	Fair
	6/30/31	36–86	Formed	Alkalin	Fair	Fair	Poor
G. S. C.	12/4/30	12–42	Soft	Acid	Fair	Poor	Fair
	1/5/31	19–67	Formed	Neutral	Good	Fair	Poor
	5/4/31	14–87	Formed	Alkalin	Good	Fair	Poor
	11/9/31	37–135	Normal	Alkalin	Good	Fair	Fair
A. M. C.	7/21/31	36–63*	Soft	Alkalin	Good	Poor	V. poor
	8/11/31	62–86	Soft	Alkalin	Good	Poor	Fair
	1/13/32	39–135	Formed	Alkalin	Good	Poor	Fair
A. C.	3/3/30	63–109	Soft	Acid	Good	Poor	Fair
	11/6/30	38–110	Formed	Neutral	Good	Fair	Fair
C. H. F.	6/29/31	45–85	Formed	Alkalin	Good	Fair	Poor
	12/14/31	43–119	Formed	Alkalin	Good	Fair	Poor
I. C. H.	12/10/29	14–62*	Soft	Acid	Fair	V. poor	Poor
	3/ 7/30	20–74	Soft	Neutral	Good	Fair	Poor
	5/16/30	45–156	Normal	Alkalin	Good	Good	Fair
	10/22/30	37–132	Normal	Alkalin	Good	Fair	Fair
G. L.	1/15/30	26–50	Soft	Neutral	Good	Poor	Fair
	2/ 6/30	36–110	Formed	Alkalin	Good	Fair	Good
	12/27/30	36–110	Formed	Alkalin	Good	Fair	Fair
E. L.	8/18/30	13–60	Soft	Acid	Fair	Fair	Poor
	9/17/30	37–85	Formed	Neutral	Good	Poor	Fair
	11/14/30	60–110	Normal	Alkalin	Good	Fair	Good
G. G. M.	12/ 1/30	38–75	Soft	Alkalin	Good	Poor	Good
	3/25/31	15–110	Soft	Alkalin	Good	Fair	Good
	4/14/31	51–108	Formed	Alkalin	Good	Fair	Good
L. A. M.	11/ 3/30	27–86*	Soft	Acid	Fair	Poor	Poor
	6/15/31	38–110	Formed	Alkalin	Good	Poor	Good
G. N.	5/16/30	60–134*	Formed	Acid	Good	Good	Poor
	6/19/30	63–111	Formed	Neutral	Good	Good	Fair
	10/ 6/30	62–116	Normal	Alkalin	Good	Good	Good
A. J. R.	3/14/30	16–110*	Formed	Acid	Good	Fair	Poor
	5/29/30	39–110	Formed	Neutral	Good	Poor	Fair
	3/13/31	39–205	Normal	Neutral	Good	Fair	Fair

RECORD 1.

DOE, DAVID.
HEALTH MEASURES TO IMPROVE: Eat slowly and only at meal times.

Wednesday, October 7, 1931.

6.30 to 6.55 P.M. Lamb, cauliflower, bread and butter, chocolate blanc mange, cookies.
7 P.M. Seeds taken to mark this meal.

Thursday, October 8.

7.15 to 7.30 A.M. Prunes, oatmeal, scrambled eggs and muffins, coffee.
8 A.M. Soft dejection with first seeds. *Initial rate 13 hrs.*
12.30 to 12.45 P.M. Lamb hash, muffins and butter, baked apple, cake.
6.30 to 6.50 P.M. Beef steak, potato, white bread and butter, vanilla ice cream.
9.30 P.M. No dejection.

Friday, October 9.

7.20 to 7.35 A.M. Pears, cream of wheat, eggs and bacon, toast, coffee.
8.25 A.M. Soft dejection with seeds.
12.35 to 12.50 P.M. Veal stew, rye muffins and butter, stewed pears, cake.
6.25 to 6.50 P.M. Haddock, rice, beets, rolls and butter, custard pie.
10.15 P.M. No dejection.

Saturday, October 10.

7.25 to 7.35 A.M. Orange, shredded wheat, mackerel, doughnut, coffee.
8 A.M. Soft dejection with last seeds. *Final rate 61 hrs.*
12.20 to 12.50 P.M. Fish chowder, pilot crackers, peach pie.
6.35 to 7.30 P.M. Celery soup, roast beef, potato, broccoli, rolls and butter, fruit salad, bar-le-duc, cream cheese and crackers, peach ice cream, and cake, coffee.
11.30 P.M. Soft dejection without seeds.

The dejections noted by patients in these first records are often of the soft type; and the "marked" evening meal in passing through the digestive system in 13 (initial) and 61 hrs. (final) signifies a rapid intestinal rate. The former erroneous ways of eating may be largely responsible for the malabsorption, but some foods should be omitted or greatly reduced, to relieve the irritability of the colon. Accordingly, still more health measures are advised, such as "eat many vegetables and sparingly of meats, cereal food and fruit" and are written at the top of a second sheet for a record of nutrition. These measures should be adopted immediately, but records should not be started for a week, in which case another appointment is given in 2 weeks. At this visit, patients generally feel better, and may have lost a few pounds. They are also likely to have noted that some dejections were formed instead of soft and, while the initial intestinal rate may still be rapid, at 14 hrs., the final rate has extended to 85 hrs. These and other changes indicate that better alimentary mixtures have improved the colonic functions (Table 1). At this time, when patients begin to make better use of the food going through them, they may also be advised to eat a small breakfast and lunch.

From now on, patients should be seen every few weeks in order to consider the state of the joints, the general condition, and the weight of the body, but more particularly for the examination of records of nutrition. Unless patients present records showing 1 and sometimes 2 daily dejections of entirely segmented feces and, more

particularly, intestinal rates of about 38 (initial) and 110 hrs. (final) or better, at these visits, they must carry out still more health measures and be seen frequently. However, others who have improved in health, strength and weight, and have normal dejections and, especially, normal rates may be seen less frequently. Whenever these patients are seen they must present a week's record of nutrition, as well as records of bi-monthly determinations of the intestinal rate and bodily weight. Besides examining these records and the condition of the joints, the state of other disorders such as anemia and hypoglycemia may be observed every few months.

To reduce the swelling, alleviate the pain and restore the action of the joints, rest, heat, massage or exercises are most beneficial if supervised by an experienced physiotherapist under a surgeon. This is because the relief of each joint is an individual problem. These measures are best applied in combination, as baking and massage alone are not often effective. The acutely painful and swollen joint must be kept quiet, and the unnecessary use of enlarged knees, wrists or phalangeal joints is likely to increase the discomfort and swelling. To assure proper rest for the vertebræ, braces or collars may be applied. In this stage, too, the use of heat should not be extreme or long continued, and massage or exercises should not be used. With the subsidence of pain and swelling, more extended and intense baking or hot fomentations, and gentle superficial massage above and below the joints may be practised. In this stage, too, patients may be taught to contract gently the muscles which control the joints, in order to improve the tone and condition of the muscles, articular cartilages and bones. If the joints are protected by traction and jointed splints to allow the greatest motion without discomfort, exercises may be tried. All of these measures increase the circulation and thus improve the nutrition of the joint. On the relief of pain and superficial swelling, the joints may be directly and more vigorously massaged, and the muscles which control them extensively exercised; but an increase of swelling is a contraindication to the use of these measures.

The Restoration and Control of Health. The results of an attempt to educate several hundred patients in the creation and control of health by anabolic nutrition to cure arthritis are shown in Table 2.

TABLE 2.—THE RESULTS OF ANABOLIC NUTRITION IN THE TREATMENT OF ARTHRITIS.

Kind.	Number.	Condition.	Number.
	Patients.		
Private	74	Healthy	43
Charity	167	Improved	75
		Improved after two trials	(7)
Total seen	241	Unimproved or worse	34
Uncoöperative	89		
			152
Total studied	152		

Women outnumbered men two to one; and while most were middle aged, a few were young and some were old. Americans of moderate intelligence predominated; and they were not only interested in new principles of health education but also exercised commendable control in correcting erroneous ways of eating. Some of the patients could not be taught or would not coöperate; and only those who brought in 5 or more records over a period of more than five months have been considered in evaluating the treatment. Of the remainder, more than one-fourth have been cured, because the swelling and pain have been entirely relieved and the motility of the joints has been generally normal. Details of the restoration of health in some of these patients are shown in Table 3. About one-half have improved and enjoy an extended sphere of activity. Some of these patients have not been treated long enough to become healthy. A few of them tried to create anabolic nutrition once, failed and became worse; and then after a while tried again and succeeded. Finally, the remainder has stayed the same or become worse. A few of these patients could not understand the principles of treatment, but most of them would not coöperate. The results obtained in the whole group are encouraging, although the relief of the disease and the prevention of relapses in more patients might have been possible if better instruction and especially a better "follow-up" could have been carried out. Ober[12] has already outlined a plan to control the health of patients with arthritis.

When a state of health is created to cure disease, the fight is only half won when arthritis is relieved; for the improved state of well-being must be subsequently controlled if the disease is to be cured. All persons are human and are likely to digress from the even, and sometimes dull, tenor of healthy living. Such digressions, if infrequent and of short duration, may not be injurious if a reserve of health has been established. To prevent another attack, it is necessary to know how well these persons control anabolic nutrition in order to remain healthy. To this end, all those instructed in these principles of treatment are required to observe the dejections and keep them normal; then to make and record tests of the intestinal rate and figures of bodily weight every few weeks; and several times a year, according to the supervision needed, they are requested to bring in records of nutrition. The response to such a request is illustrated in Record 2. At one of these visits, a comprehensive and exact examination of the body, joints and various specimens may be carried out to assure these persons of good health. Details of treatment of a few patients and healthy persons who have endeavored to create and control health by anabolic nutrition are described in the following reports. The minor digressions from right eating or living that produced malabsorption and made the patients worse are especially interesting and are written in italics.

TABLE 3.—THE RESTORATION AND CONTROL OF HEALTH BY PATIENTS FROM ANABOLIC NUTRITION.

Initials.	Age and sex.	Diagnosis, type and duration of arthritis.	Erroneous ways, excesses, or deficiencies of food consumption.	Condition, weight, feces and intestinal rate during treatment (the 4 items are listed consecutively in each column).				
				First week.	Second month.	Sixth month.	First year.	Second to fourth years.
F. A.	41 F	Clin., hypert. 10 yrs.	Fruit +, laxatives +	Same, 135 lbs. Soft, 12–60 hrs.	Same, 135 lbs. Nor., 86–123 hrs.	Improved, 139 lbs. Nor., 37–144 hrs.	*Well*, 138 lbs. Nor., 38–132 hrs.	
J. M. B.	58 F	*X*-ray., hypert. 1 yr.	Irregular +, fruit +	Same, 155 lbs. Formed, 14–111 hrs.	Impr., 152 lbs. Formed, 38–120 hrs.	Worse, 157 lbs. Soft, 13–61 (food + +)	*Well*, 155 lbs. Nor., 39–110 hrs.	
R. B.	52 F	Clin., arth. 2 yrs.	Foods +, fast +, laxatives +	Same, 168 lbs. Soft, 15–89 hrs.	Same, 174 lbs. Soft, ... (food +)	Impr., ... Formed, ...	....	*Well*, 154 lbs. Nor., ...
J. P. B.	38 M	*X*-ray., hypert. 8 yrs.	Cereals +, meats +, fast +, vegetables −	Same, 150 lbs. Soft, 13–63 hrs.	Same, 147 lbs. Formed, 39–110 hrs.	....	*Well*, 167 lbs. Nor., ...	
D. B.	33 M	Clin., arthr. 21 yrs.	Fast +, sweets +, meats +	Same, 132 lbs. Soft, 48–72 hrs.	Same, 142 lbs. Formed, 73–98 hrs.	Impr., 145 lbs. Nor., 49–97 hrs.	*Well*, 151 lbs. Nor., 60–110 hrs.	
M. C.	36 F	Clin., arthr. 1 yr.	Fast +, food +, laxatives +	Same, 115 lbs. Soft, ...	Impr., 121 lbs. Soft, 48–131 hrs.	Impr., 123 lbs. Nor., 39–144 hrs.	Worse, 122 lbs. Soft, 15–87 (fruit +)	
R. C.	44 F	*X*-ray, hypert. 1 yr.	Food −, meat −, laxatives +	Same, 138 lbs. Formed, 94–108 hrs.	Impr., 143 lbs. Nor., 15–140 hrs.	*Well*, 137 lbs. Nor., 94–180 hrs.	*Well*, 139 lbs. Nor., 109–157 (meat −)	*Well*, 140 lbs. Nor., 109–157 (meat −).
S. D.	49 F	*X*-ray, hypert. 1 yr.	Irregular +, fast +, fruit +, laxatives +	Same, 165 lbs. Soft, 14–74 hrs.	Impr., 163 lbs. Formed, 38–87 hrs.	Impr., 159 lbs. Nor., 41–140 hrs.	*Well*, ... Nor., ...	
M. F.	53 F	*X*-ray, hypert. 5 yrs.	Foods +, laxatives +	Same, 146 lbs. Formed, 17–126 hrs.	Same, 144 lbs. Nor., 41–135 hrs.	Worse, 141 lbs. Soft, 15–63 (fruit +)	....	*Well*, 144 lbs. Nor., 41–113 hrs.
I. F.	54 F	*X*-ray atrophic 1 yr.	Food +, fast +, irregular +	Same, 151 lbs. Soft, 20–38 hrs.	Impr., 150 lbs. Nor., 39–144 hrs.	Impr., 149 lbs. Nor., 37–159 hrs.	*Well*, 147 lbs. Nor., 37–133 hrs.	*Well*, 145 lbs. Nor. 38–143 hrs.
F. F.	40 F	Clin. arth. 1 yr.	Food + cereals + laxatives +, vegetables −	Same. 164 lbs. Soft, 15–87 hrs.	Impr., 161 lbs. Nor., 36–110 hrs.	Impr., 165 lbs. Nor., 61–132 hrs.	*Well*, 169 lbs. Nor , 36–138 hrs.	*Well*, 169 lbs. Nor., 13–110 hrs.
E. F.	49 F	*X*-ray, atroph. 1 yr.	Fast +, irregular +, cereals +, vegetables +	Same, 134 lbs. Soft, 13–67 hrs.	Same, 133 lbs. Formed, 25–135 hrs.	Impr., 135 lbs. Nor., 37–135 hrs.	*Well*, 134 lbs. Formed, 18–110 hrs.	
E. H.	54 F	*X*-ray, hypert. 7 yrs.	Fast +, sweets +, oil +	Same, 172 lbs. Soft, 13–64 hrs.	Same, 164 lbs. Soft, 48–59 hrs.	Impr., 162 lbs. Formed, 15–109 hrs.	*Well*, 159 lbs. Nor., 60–135 hrs.	*Well*, 157 lbs. Nor., 39–109 hrs.
A. I.	64 F	Clin., arth. 5 yrs.	Food −, laxatives +	Same, 106 lbs. Formed, 12–134 hrs.	Impr., 106 lbs. Nor., 36–108 hrs.	Impr., 112 lbs. Nor., 38–134 hrs.	*Well*, 116 lbs. Nor., 39–135 hrs.	*Well*, 116 lbs. Nor., 38–110 hrs.
M. McL.	35 F	Clin., arth. 1 yr.	Fast +, irregular +, cereals +, sweets +	Same, 174 lbs. Soft, 14–51 hrs.	Same, 163 lbs. Formed, 25–108 hrs.	Impr., 162 lbs. Nor., 38–120 hrs.	*Well*, 161 lbs. Nor., 39–122 hrs.	*Well*, 158 lbs. Nor., 39–120 hrs.
T. O'B.	31 M	Clin., hypert. 2 yrs.	Fast +, irregular +, fruit +	Same, 148 lbs. Soft, 36–97 hrs.	Same, 145 lbs. Nor., 36–136 hrs.	Impr., 144 lbs. Nor., 38–133 hrs.	*Well*, 142 lbs. Nor., 39–134 hrs.	*Well*, 150 lbs. Nor., 61–120 hrs.
M. R.	44 F	Clin., hypert. 3 yrs.	Meat −, cereals +, laxatives +, vegetables −	Same, 144 lbs. Soft, 36–87 hrs.	Same, 143 lbs. Soft, 13–88 (fruit +)	Impr., 153 lbs. Nor., 38–112 hrs.	*Well*, 153 lbs. Nor., 40–134 hrs.	*Well*, 155 lbs. Nor., 38–93 hrs.
W. S.	43 M	*X*-ray, hypert. 1 yr.	Fast +, cereals +, meat +, vegetables −	Same, 210 lbs. Soft, 16–144 hrs.	Same, 206 lbs. Soft, 25–117 hrs.	Impr., 199 lbs. Nor., 41–133 hrs.	*Well*, 191 lbs. Nor., 61–134 hrs.	*Well*, 183 lbs. Nor., 63–135 hrs.
E. W.	53 F	*X*-ray, atroph. 2 yrs.	Fast +, irregular +, fruit +	Same, 154 lbs. Soft, 12–39 hrs.	Same, 151 lbs. Formed, 21–112 hrs.	Impr., 150 lbs. Nor., 39–132 hrs.	*Well*, 143 lbs. Nor., 40–134 hrs.	*Well*, 141 lbs. Nor., 43–75 hrs.
C. W.	60 F	Clin., arth. 12 yrs.	Fruit +, fat +	Same, 158 lbs. Soft, 38–63 hrs.	Same, 157 lbs. Nor., 38–110 hrs.	Impr., 155 lbs. Nor., 14–110 hrs.	*Well*, 155 lbs. Nor., ...	*Well*, 150 lbs. Nor., ...

RECORD 2.

JONES, JOSEPHINE

HEALTH MEASURES TO CONTINUE: Eat a small breakfast and lunch, sparingly of meat, fat and cereal food, and fruit according to absorption. Determine the intestinal rates and weights in May and June and bring in a complete record in July.

	Rates.	*Weights.*
May	37 to 132 hrs. and 63 to 134 hrs.	137, 139
June	61 to 120 hrs. and 57 to 156 hrs.	138, 138

Wednesday, June 28, 1931

7 to 7.45 P.M. Cold consommé, cracker, roast chicken, potato, beet greens, tomato and lettuce salad, bar-le-duc cheese and crackers, demi-tasse.
7.45 P.M. Seeds taken to mark this meal.

Thursday, June 29.

8 to 8.10 A.M. Corn muffins and butter, coffee.
9.30 A.M. Normal dejection.
1.30 to 1.50 P.M. Cheese souffle, asparagus salad, roll and butter, cocoa, cantaloupe melon.
7.05 to 7.30 P.M. Salmon, peas, spinach, bread and butter, raspberry mousse, cake, demi-tasse.

Friday, June 30.

8.10 to 8.25 A.M. Toast and butter, coffee, milk.
10.15 A.M. Normal dejection.
1.15 to 1.40 P.M. Tomato omelette, potato, roll and butter, fruit salad.
7.30 to 8.30 P.M. Cold clam broth, steak, potato, broccoli, roll and butter, asparagus on toast, strawberry ice cream, cake, demi-tasse.
11 P.M. Normal dejection with first seeds. *Initial rate 50 hrs.*

Saturday, July 1.

8.30 to 8.45 A.M. Wheat gems and butter, coffee, milk.
9 A.M. Formed dejection with seeds.
1.30 to 1.35 P.M. Fish chowder, crackers, cup custard.
7 to 7.30 P.M. Duck, jelly, potato, string beans, apricot salad, demi-tasse.
10.30 P.M. No dejection.

Sunday, July 2.

8.30 to 8.45 A.M. Brown bread and butter, coffee.
10.15 A.M. No dejection.
1.45 to 2.05 P.M. Scrambled eggs and bacon, roll and butter, cocoa, asparagus salad, prune whip.
7 to 7.30 P.M. Roast beef, potato, peas, roll and butter, apple pie.
10 P.M. Normal dejection with seeds.

Monday, July 3.

8.30 to 8.45 A.M. Toast and marmalade, coffee, milk.
9.45 A.M. Normal dejection with seeds.
1 to 1.20 P.M. Bouillon, welsh rarebit, spinach, strawberries and cream, cake.
7 to 7.30 P.M. Lamb, potato, cauliflower, roll and butter, rennet, pear, demi-tasse.
10.30 P.M. Small normal dejection with seeds.

Tuesday, July 4.

8 to 8.30 A.M. Corn muffins and butter, coffee.
10 A.M. Normal dejection with last seeds. *Final rate 134 hrs.*
1.30 to 1.45 P.M. Shirred egg, peas, roll, milk, raspberry sherbet, cake.
7 to 7.30 P.M. Cold consommé, lamb chop, potato, spinach, roll and butter, asparagus on toast, peach ice cream, demi-tasse.

Wednesday, July 5.

8.10 to 8.20 A.M. Puffed wheat with milk and sugar, coffee.
10.30 A.M. Normal dejection without seeds.

CASE 1.—Mr. A. M. C., American, aged 45, married, salesman, has had pain in the spine and pain and swelling of the wrists for 2 years. Roentgen ray diagnosis, hypertrophic arthritis. Several years ago used to eat too much and too fast, an excess of sweet and cereal food, and weighed 175 pounds. Has taken laxatives regularly for many years. Weight now 135 pounds. Indigestion and malnutrition shown by soft, alkalin feces, in which protein digestion is fair, fat poor, and starch very poor.

July 21, 1931. Advised to omit laxatives, eat slowly, fruit at lunch and dinner, and try to deject twice daily. Also to rest, use hot soaks t. i. d. and take acetylsalicylic acid p. r. n.

July 28, 1931. Weight 132¼ pounds. Regular without laxatives during the week, but has had soft dejections and a rate of 36 and 63 hrs. To eat less fruit.

August 11. Feels stronger and sleeps better. Weight reduced to 131¼ pounds. Dejections generally regular and formed, with a rate of 62 to 86 hrs. Good diet.

September 1. Less swelling and pain in joints. Weight 131 pounds. Dejections regular and normal, rate 62 to 135 hrs. To eat many vegetables.

October 11. Back at work again and travelling about. Swelling and pain increased from *too much use of limbs*. Weight 130 pounds. Rate of 63 and 87 hrs. To eat slowly, less fruit, but according to absorption. Also to get more rest and take digestive tablets.

December 1. Continues to have pain but swelling is reduced; also sleeps soundly and weight is increased to 134 pounds. Rate 63 and 111 hrs. Good diet.

March 7, 1932. *Ate some decomposed food*, had diarrhea for a week, lost weight, and had a return of pain and swelling. Rates in February 41 to 107 and 63 to 136 hrs. To eat sparingly of fat food and fruit according to absorption.

May 21. Has had an opportunity to rest more recently, pain and swelling have subsided and weight is 132 pounds. Rate 63 to 132 hrs. To continue rest and same diet.

August 4. Improvement continues and weight continues at 132. Rate in June 64 to 133, July 63 to 134 hrs. Now dejections are generally formed and normal and rate is 63 to 110 hrs.

CASE 2.—Mrs. G. N., American, aged 46, housewife, has had pain and swelling of hands and knees for 10 years. Roentgen ray diagnosis, hypertrophic arthritis. Weight 145 pounds. Used to eat frequently between meals, and especially of sweet stuff. Now eats too much meat, bread and fat food, and too few vegetables. Indigestion shown by formed, acid feces, in which protein and fat digestion are fair, but starch digestion is poor.

May 15, 1930. Advised to reduce protein, fat and cereal food, and eat more vegetables.

May 22. About the same. Dejections irregular, with a rate of 60 to 134 hrs. Weight 145 pounds. Is eating too much cereal food and too few green vegetables.

June 19. About the same, but is sleeping better. Weight 144 pounds. Dejections still somewhat irregular and formed, with a rate of 63 to 111 hrs. Eat a light breakfast and lunch, less meat and fish, and fruit according to absorption.

September 4. While abroad, *ate irregularly*, had regular but soft dejections. Rate not determined. Pain and swelling became worse. Weight 145 pounds. Since returning, has returned to diet and dejections have become irregular but normal, rate 70 to 165 hrs. To eat more fruit but according to absorption.

October 6. Improved, swelling reduced and pain much relieved. Weight 144 pounds. Dejections regular and normal again, with a rate of 62 to

116 hrs. In a health test the physical examination was negative, and blood pressure 113/80. In laboratory tests the hemoglobin was 72% (Newcomer); corpuscle count, 4,200,000; leukocyte count, 8600; differential count: polymorphonuclears, 65%; lymphocytes, 26%; myelocytes, 0%; endothelials, 7%; eosinophils and basophils, 2%. Non-protein nitrogen, 32 mg. and sugar, 123 mg. Feces normal, alkalin, protein digestion good, fat good, starch fair. Urine normal.

January 8, 1931. Much improved, pain and swelling about gone. Weight 145 pounds. Had a cold recently, took laxatives and enemata and had irregular, soft dejections for a while. After dejections became normal they were regular, with a rate of 63 to 156 hrs. To eat a light breakfast and lunch, many green vegetables and more fruit, but according to absorption.

March 5. About well, gets about as she wishes without pain, and swelling about gone. Weight increased to 148 pounds. Dejections regular and normal, rate 63 to 111 hrs. To eat very sparingly of cereal and fat food. September 18. *Well.* Weight 147 pounds. Rate 62 to 132 hrs.

CASE 3.—Mrs. G. S. C., American, aged 52, housewife, has had pain and swelling of the neck, shoulders and knees for 10 years, and Roentgen ray diagnosis of hypertrophic arthritis. Weight now 139 pounds. Eats irregularly, too much cereal food especially, and takes laxatives regularly. Indigestion and malnutrition shown in first naturally dejected stool by soft, strongly acid feces, a fair protein digestion, but a poor fat, and very poor starch digestion.

November 27, 1930. Advised to eat slowly, only at meals, a small breakfast and lunch; to omit oranges and grapefruit but eat other fruit at lunch, and try to deject twice. Rest advised, and also acetylsalicylic acid p. r. n. Physiotherapy advised.

December 4. During the week the condition has remained unchanged and weight is 139 pounds. Dejections regular but soft, with a rate of 12 to 42 hrs. A reduction of cereal, fat and sweet food advised.

January 5, 1931. Still has pain and swelling of the joints and weight is unchanged at 139 pounds. Feces formed at times, with a rate of 19 to 87 hrs. Eats too much cereal food and too few green vegetables especially.

March 9. Began to improve, went on a visit, *ate irregularly and too much rich food* and became worse. Dejections regular, but soft, with a rate of 14 to 39 hrs. To eat only at meals, a light breakfast and lunch, many leafy vegetables, and fruit according to absorption.

June 9. Continues to improve, has less pain, and swelling of joints had entirely subsided. Gets about comfortably. Weight 144 pounds. Dejections regular, generally formed, alkalin, with a rate of 46 to 133 hrs. To eat sparingly of fat and starchy food.

September 9. Has gained in health, but has been *eating irregularly and too much cereal food lately*. Had a fair rate of 12 to 113 hrs. in August, but recently has had many soft dejections and a rate of 36 to 63 hrs. Advised to eat only at meals and less cereal food.

November 9. Much improved again. Weight reduced to 142, dejections regular and often normal, with a rate of 37 to 135 hrs.

March 16, 1932. Continued to improve up to a month ago, when dejections became soft, with a rate of 15 to 61 hrs. There has been a slight return of pain and swelling. Weight reduced to 136 pounds. Record shows ingestion of *too much rich food and cereal food.*

December 7. Is slowly becoming better nourished and healthier. Weight increased to 139 pounds. Has had formed and normal dejections generally and rates of about 63 to 134 hrs. Now brings in a record of 18 to 111 hrs. To eat less fat and cereal food, more green vegetables, and less fruit but according to absorption.

February 27, 1933. Has made a marked improvement. Weight reduced to 135 pounds. Has had normal dejections generally, and on tests of the rate every few weeks has generally had rates of about 63 to 134 hrs. Brings in a record with regular and normal dejections and a rate of 87 to 164 hrs. To eat more fruit especially, but according to absorption.

CASE 4.—Miss E. W., American, aged 53, has had pain and swelling of the knees for 2 years. Roentgen ray diagnosis, atrophic arthritis. Weight 154 pounds. Now eats too fast, irregularly, and too much fruit.

October 31, 1929. Advised to eat a small breakfast and lunch, but a substantial dinner at night. Also to omit oranges and grapefruit and eat other fruit at lunch only.

November 6. About the same, weight reduced to 150 pounds. Dejections formed, with a rate of 15 to 135 hrs. To eat less cereal food.

December 18. Condition improved. Weight 148 pounds. Rate 36 to 156 hrs. Good diet.

February 12, 1930. Continues to improve. Weight 147 pounds. Rate 40 to 156 hrs.

July 2. *Well.* Weight 142 pounds. Rate 39 to 110 hrs.

December 10. Continues *well.* Weight 146 pounds. Rate 38 to 110 hrs. Good diet.

April 15, 1931. Continues *well.* Weight 149 pounds. Rate 39 to 111 hrs.

October 14. Continues *well.* Weight 149 pounds. Rate 41 to 113 hrs.

February 17, 1932. Continues *well.* Weight 149 pounds, and has had rates of 39 to 111, 39 to 113, 39 to 111 hrs.

November 30. Continues *well.* Weight 145 pounds, and has had rates of 41 to 112, 40 to 111, 41 to 113 hrs.

March 29, 1933. Continues *well.* Weight 145 pounds. Rate 39 to 123 hrs.

The Operation of the Proximal Colon. "The wonder is not that structural imperfections and functional disharmonies should develop in proportion to our numbers, but rather that so many of us escape harm altogether and enjoy good health. . . . The solution of our problem of life is a fuller knowledge of the use and working of those parts of our bodies most apt to give way under our modern ways of living—the use of such structures as the great bowel. And when we have replaced our ignorance by real knowledge we shall be in a position not to adapt our bodily structures to our mode of living, but our mode of living to our bodily structures. . . . The bowel is not a useless or superfluous organ, but one which we in our ignorance are maltreating." (Keith.[13])

To adapt our ways of eating and mode of living to the complex and delicately adjusted control exercised by the proximal colon, certain requirements must be fulfilled. To this end, the food ingested by a healthy person may be somewhat similar to that in Record 2. One requirement for this action is the consumption of a small amount of food at breakfast and lunch but a substantial amount at dinner; although a small combined breakfast-lunch in the middle of the morning and a substantial dinner in the evening is advisable for obese and sedentary patients. On the contrary, the consumption of insufficient food does not appear to supply the needs of the tissues for nourishment and leave a residue for daily

defecation; thus the dejections are irregular, the intestinal rate abnormally extended, and the patient malnourished. The weight and value of the food may vary from 50 to 100 gm. of protein, 50 to 100 gm. of fat, and 150 to 200 gm. of carbohydrate (1500 to 2500 large calories), according to the age, sex, size and activity of the person. While the amount of food is small, if the intestinal rate is normal there is a large amount of nutritive material in the digestive system. Everyone is instructed to attempt defecation an hour or two after breakfast and again at bedtime, irrespective of an impulse. One and occasionally 2 days without a dejection improve the absorption if the intestinal rate has been too rapid. A second requirement is the thorough mastication of the food; each mouthful of starchy food especially should be made fluid with saliva before it is swallowed. A third requirement is that the diet be "complete," as avitaminosis sometimes causes diarrhea.[14] A fourth requirement is that many vegetables be ingested to make the aliment alkalin. Forman, Pennington and Funkhouser[15] found the soft feces often had an acid reaction of pH 5 to pH 6.5; whereas the segmented stool had an alkalin reaction of pH 7 to pH 7.5. A fifth requirement is to eat fruit according to absorption. As the action of the colon is not known until after the dejection, which generally occurs after breakfast, the ingestion of fruit is advised at lunch and sometimes dinner. Some patients get an irritable colon from the ingestion of too much fruit, especially the citrous fruits; whereas, when the irritability of the colon has been relieved, enough fruit must be ingested to produce regular defecation and prevent the intestinal rate from becoming abnormally extended. A sixth requirement is the omission of all laxatives, oils or enemata; because regular and normal dejections are produced by the regulation of normal foods.[16] Furthermore, Magnus[17] has observed that the normal antiperistaltic waves of the proximal colon in animals are inhibited by food containing senna.

Two glasses of water or a corresponding amount of fluid are advised at each meal, one on arising and one at bedtime, under ordinary conditions. Moderation in the use of beverages and malted or spirituous liquor and tobacco does not appear injurious. Finally, 8 hrs. of sleep are advocated, and this is often accomplished if some physical exercise is taken outdoors every day. Exercise is greatly restricted in extremely deficient patients, however, as the intestinal rate is likely to be rapid; and these patients are advised to rest once or twice during the day and try to sleep more than 8 hrs. at night.

The Wisdom of the Body, the Conscious Colon, and Health. " . . . 'The circuit of the blood is accomplished, now more rapidly, now more slowly, according to the temperament, age, etc., of the individual, to external and internal circumstances, to naturals and non-naturals—sleep, rest, food, exercise, affections of the mind and the

like.'" . . . through the wisdom of the body . . . . "The heart has a marvelous power of adapting its work and its performance to the needs of the body." (Starling.[18])

Just as the circulation changes according to sleep, rest, food, exercise and affections of the mind and the like, so the cycle of digestion and absorption of the aliment, regulated by the same kind of "wisdom of the body," likewise varies according to our ways of eating and living. Then again, as the heart adapts its work to the needs of the body, so does the digestive system adapt its performance to the requirements of the tissues for nutrient substances. In this way the functions of the digestive system operate as a perfect nutritive apparatus, in which the course of the aliment is largely controlled by stimuli within and without on the dual and conscious action of the digestive pouches. Thus the primary pouch—the stomach—automatically acts and reacts according to the ingested mixture. For proper food is normally churned with the digestive fluids to promote mixing and digestion; but an extremely unsuitable mixture is abnormally expelled, by vomiting, to prevent the absorption of injurious substances. Moreover, the secondary pouch—the proximal colon—acts in a similar way; for here, in animals, the aliment is normally worked over by waves of peristalsis and antiperistalsis, and then "a segment from its contents is every now and then nipped off by a ring of constriction, and carried away to be moulded in its further passage down the colon to the firm fecal nodule."[19] But a rapid and propulsive passage of the contents which results in diarrhea, and one probably due to irritant products, has also been observed.[20] In man, too, the aliment is passed through the colon by two kinds of action. One is the movement of Fischl and Porges,[21] by which small, uniform segments are passed slowly through the distal colon. This act, similar to the normal action in animals, evidently signifies the normal action of the colon. The other is the mass movement of Holzknecht,[22] by which large, irregular masses are rapidly passed through the colon. This rapid propulsive act may be regarded as resembling vomiting, and obviously abnormal. Each function molds the colonic contents in a significant way; for from right eating and living one function produces the entirely segmented feces, and from erroneous ways another action molds the soft and formless stools.

From this point of view the colon operates with a conscious capacity and may be made to serve as an exact and delicately adjusted control, especially of proper ways of eating. Moreover, through "the wisdom of the body" and the "consciousness" of the colon, the soft feces serve as a definite means to determine intestinal indigestion as an early and slight disorder of the nutritive apparatus.[4] On the other hand, the entirely segmented feces produced by the correction of erroneous ways of eating indicate that the aliment has completed its cycle of digestion and absorption. Thus a morbid

process is replaced by a vital process for the creation of a heretofore unrecognized condition of the human body—an exact state of health from anabolic nutrition.

Summary. A failure of nutrient substances to construct healthy bone and cartilage, or a metabolic disorder, has often been considered as the cause of arthritis. In many ways health is a vague and variable condition; but from the operation of the digestive system as a perfect nutritive apparatus, through an understanding of the wisdom of the body, a process evidently becomes effective which creates an exact state of health. Such a process is produced by the correction of erroneous ways of eating and living, to operate properly the "secondary digestive pouch," the proximal colon; for this function finally molds the intestinal contents into the uniform masses of the entirely segmented or normal feces and produces normal intestinal rates. As these indices signify complete digestion and absorption, any other kinds of feces or rates are an indication of the passage of nutritive material through instead of into the body and of intestinal indigestion. As the normal indices imply the assimilation of improved nutrient substances by cells, the process created by their production has been called "anabolic nutrition."

In an attempt to create anabolic nutrition to cure arthritis, several hundred patients have been educated; but as a third of them would not coöperate, the value of the treatment is based in this study on 152 patients. Of this number, health has been restored in more than one-fourth, improved in one-half, and remained the same or became worse in the others. In some of those who improved, health is likely to be restored by more prolonged treatment; in a few, one attempt to create anabolic nutrition failed and they became worse, but later another attempt proved beneficial. In those who remained the same or become worse, either an understanding of the principles or coöperation could not be secured. For healthy persons relieved of arthritis to prevent a recurrence, they must be supervised; and therefore they are required to make and record tests of the intestinal rate and bodily weight every few weeks and return to the office or health class with records of nutrition every few months. Thus they may control health by anabolic nutrition, and cure arthritis.

REFERENCES.

1. Nichols, E. H., and Richardson, F. L.: J. Med. Res., **21**, 149, 1909.
2. Minot, G. R.: New England J. Med., **208**, 1285, 1933.
3. Fletcher, A. A., and Graham, D.: Am. J. Med. Sci., **179**, 91, 1930.
4. Burnett, F. L.: Boston Med. and Surg. J., **184**, 371, 415, 1921.
5. Webster's New International Dictionary; W. T. Harris and F. S. Allen, Springfield, Mass., G. and C. Merriam Company, 1924.
6. Burnett, F. L.: New England J. Med., **205**, 251, 1931.
7. Burnett, F. L.: Am. J. Med. Sci., **166**, 415, 1923.
8. Burnett, F. L.: New England J. Med., **199**, 321, 1928.
9. Burnett, F. L., and Howe, P. R.: J. Am. Med. Assn., **88**, 1705, 1927.

10. Wolbach, S. B., and Howe, P. R.: Arch. Path. and Lab. Med., **1**, 1, 1926.
11. Rinehart, J. F., Connor, C. L., and Mettier, S. R.: J. Exp. Med., **59**, 97, 1934.
12. Ober, F. R.: New England J. Med., **206**, 393, 1932.
13. Keith, A.: Lancet, **2**, 1047, 1925.
14. Mellanby, E.: Brit. Med. J., **1**, 515, 1926.
15. Forman, W. H., Pennington, W. E., and Funkhouser, A. G.: Trans. Sec. Gastro-enterol. and Proctol., Am. Med. Assn., 1925.
16. Burnett, F. L.: J. Am. Med. Assn., **83**, 996, 1924.
17. Magnus, R.: Arch. f. d. ges. Physiol., **122**, 251, 1908.
18. Starling, E. H.: Brit. Med. J., **2**, 685, 1923.
19. Elliott, T. R., and Barclay-Smith, E.: J. Physiol., **31**, 272, 1904.
20. Cannon, W. B.: J. Am. Med. Assn., **59**, 1, 1912.
21. Fischl, L., and Porges, F.: Münch. med. Wchnschr., **58**, 2064, 1911.
22. Holznecht, G.: Ibid., **56**, 2402, 1909.

A SURVEY OF HUMAN INTESTINAL PROTOZOAN PARASITES IN PHILADELPHIA.

By H. Corwin Hinshaw, Ph.D., M.D.,
FELLOW IN MEDICINE, MAYO FOUNDATION; FORMERLY ASSOCIATE PROFESSOR OF PARASITOLOGY, AMERICAN UNIVERSITY OF BEIRUT, BEIRUT, LEBANON REPUBLIC (SYRIA),
AND
Ethel M. Showers, R.N.,
PHILADELPHIA, PA.

(From the Gastro-intestinal Section of the Medical Clinic, University of Pennsylvania Hospital.)

Relatively little information is available as to the frequency and importance of infestation with intestinal protozoa among residents of temperate climates who dwell at home under the conditions of modern city life. It is well recognized, however, that such infestations are significantly frequent in southern sections of the United States and in warmer climates throughout the world; also, that they are exceedingly common in the stools of individuals who are living in large groups such as armies[1] or institutions,[2] and in those who lack the advantages of modern city sanitation.[3] Andrews and Paulson,[4] in 1931, were able to find *Endamœba histolytica* in only 0.3% of a group of 312 individuals living under modern home conditions in Baltimore. This is in striking contrast to the findings of 67% in a group of 91 soldiers by Kofoid and Swezy,[5] and of 11.4% in the rural districts of Tennessee by Meleney, Bishop and Leathers,[3] and to the estimate of Craig[6] that between 5 and 10% of the entire population of the United States carry this potentially dangerous parasite.

It is possible that some surveys have been made during periods of silent epidemics, it is probable that the incidence of cases varies from time to time in the same locality, and it is certain that the facilities for transmission vary widely in different strata of the population. The greater ease of obtaining material from institutionalized

groups has led to a disproportionate study of such groups. The recent widespread epidemic traced to Chicago emphasizes the fact that there is a constant potential menace whenever and wherever individuals congregate. The present survey, made during the winter of 1932–1933 and just preceding the Chicago epidemic, demonstrates that other cities as well possess an adequate number of carriers to effect an equal dissemination if facilities are offered. Public health practices should be amended to insure the destruction of ameba cysts along with the much less resistent pathogenic bacteria.

The present investigation was undertaken to learn how frequently intestinal protozoa should be anticipated in this locality among patients entering the medical wards of a hospital. We know of no similar survey of Philadelphia or its immediate vicinity. Interest is added by comparison of these findings with those obtained by one of us (Hinshaw, to be published) in a similar but more extensive survey in the subtropical climate and oriental living conditions of Beirut, Lebanon Republic, Syria.

Material and Methods. Specimens were requested of unselected patients upon admission to the wards of the Medical Clinic of this hospital, regardless of the nature of their complaints. Additional specimens were submitted from patients in whom intestinal disease was suspected, including especially outpatients visiting the gastro-intestinal section: none of these, however, carried *E. histolytica*, so that this departure from our original plan of studying an unselected group had no effect in increasing the incidence of this infestation.

Specimens (535) were examined from 368 patients (average 1.5). The frequent use of mineral oil to avoid constipation in hospital patients often made subsequent specimens unsuitable for study. Among those yielding no intestinal protozoa an average of 1.2 specimens per patient were studied, while for those found to have some kind of infestation 2.1 specimens per individual were secured. Part of this difference is accounted for by the increased interest of the clinicians in the latter group. Study of the tabulations in this paper demonstrates, as has been pointed out before, that with successive specimens from a single patient there is a tendency to discover a larger variety of organisms. It has been estimated that only one-third to one-half of existing infestations are revealed by a single stool examination: their identification may be increased to 80% or better by the proper study of 4 to 6 formed specimens or by the examination of 2 or 3 stools secured after the use of a saline laxative.

The search for motile amebæ requires an arrangement by which the patient can defecate in the laboratory and the specimen be examined immediately; also such study is subject to considerable error in that the motile forms possess less definite features for identification and in that they require more skill and experience for their interpretation. Furthermore, they require the constant presence in

the laboratory of an experienced parasitologist and yield no permanent preparation which can be studied subsequently. For these reasons we chose to base our survey on a study of the encysted forms in stained smears.

The specimens were usually obtained without a cathartic, and specimens following the administration of oily laxatives were always discarded. Although the smears were made as promptly as possible, usually within ½ hr. after defecation, such prompt examination of formed stools for the cysts is not essential. Elsewhere we have frequently examined stools which were mailed from considerable distances. We have also sent stools by air mail from Beirut, Syria, to Hoechst, Germany, where the viability of the cysts was proven by the successful infection of dogs after a transit of over 2000 miles.

Flagellates are much more conspicuous in the active motile state than when stained, being readily overlooked in the latter condition. Their specific identification, however, may be easier when they are stained.

Magath and Ward[7] carefully compared several methods of examining for intestinal protozoa, and expressed a preference for the study of fresh preparations of liquid stools obtained after a saline purge. Their facilities and skill, however, cannot be duplicated in the average instance, and for such a study as we have made, under ordinary conditions in a large general hospital, we believe that the staining method will yield more dependable results.

Method. Smears of saline emulsions of feces were made on flamed clean slides with a mucilage brush and fixed immediately while moist in hot (60° C) Schaudinn's fluid, in which they remained for 15 min. They were then placed for 10 min. each in 50 and 70% alcohol, strongly colored with iodin. Hydration was accomplished by passage through 50 and 30% alcohol and distilled water. The smears were then mordanted for 10 to 20 min. in a 2% solution of iron alum held at 30–40° C, rinsed in distilled water and stained in a ripened 0.5% solution of hematoxylin for a similar length of time at a similar temperature. Differentiation was carried out under the microscope in a 1% solution of iron alum. The slides were next thoroughly washed in running water for 20 to 30 min. and dehydrated by passage through 30, 50, 70, 90, 95 and 100% alcohol, each for about 5 min.; then left in xylol for 5 min. and mounted in balsam, using a thin coverglass. The smears were systematically searched through an oil-immersion lens.

Results. *Endamœba histolytica* is the only ameba of man the pathogenicity of which has been proved, and it is, therefore, of the greatest clinical interest. Its presence is at least potentially dangerous both to the individual and to his associates. Only 1 of our patients was suffering from amebic dysentery, while in the others no clear association could be made out between the presence of the parasites and the patient's symptoms. In this paper we are not attempting an

evaluation of the clinical significance of the organism concerned. It was found in 4 of the 368 patients studied. In 2 of them no other parasites were found; in 1 *Endolimax nana* was associated and in the other, *Giardia intestinalis*, *Endamœba tenuis*, and *E. nana* were also present. Three of the 4 cases were diagnosed by the finding of typical cysts of *E. histolytica*. The remaining case exhibited only motile amebæ and their identity was clearly established by their appearance and activity, their ingestion of numerous erythrocytes, and their great concentration in the ulcers of the rectum and sigmoid, which were visualized through the sigmoidoscope. Scrapings from the margins of these ulcers yielded great numbers of the typical amebæ. Specific therapy (emetin-bismuth-iodid) resulted in prompt and total relief of the dysentery. Numerous Charcot-Leyden crystals also were present in these specimens.

We do not believe that it is always possible to identify with certainty large motile amebæ found in stools, especially if the specimen be cold, with impaired motility and scarcity of organisms. Three such cases must be recorded in this series in which the specific differentiation between *E. histolytica* and *E. coli* could not be safely made and additional specimens were unfortunately impossible to secure. In each of these cases we were of the opinion that they were probably *E. histolytica*.

Endamœba coli was found in 18 patients, from whom a total of 33 specimens were studied. We have grouped the classical cysts together with those forms described by Kofoid and Swezy[8] as *Councilmania lafleuri*. We have never found a case demonstrating the classical forms which did not also yield the *C. lafleuri* types on further study, and all intermediate forms have been frequently observed in this and in other more extensive studies. The association of *E. coli* with other organisms is represented in the following table:

TABLE 1.—INCIDENCE OF E. COLI IN STOOLS.

	No. cases.	No. specimens.
E. coli alone	6	6
E. coli and Blastocystis	1	1
E. coli and Endolimax nana	2	2
E. coli, E. nana and Blastocystis	6	14
E. coli, Trichomonas and Blastocystis	1	6
E. coli, Chilomastix and Blastocystis	1	1
E. coli, Giardia, Iodameba and E. nana	1	3
Total occurrence of E. coli	18	33

The incidence of infection in the total group of patients was 4.9%.

Endolimax nana, a small and inconspicuous ameba of man, was the most frequently encountered of all. We have recorded it 131 times in 64 patients. Its association with other organisms is indicated in Table 2, p. 112.

TABLE 2.—INCIDENCE OF E. NANA.

	No. cases.	No. specimens.
E. nana alone	9	14
E. nana and Blastocystis	28	52
E. nana and E. tenuis	6	8
E. nana, E. tenuis, and Blastocystis	4	9
E. nana, E. tenuis, Giardia and Blastocystis	2	12
E. nana, E. tenuis, Iodameba and Blastocystis	1	1
E. nana and Iodameba	1	3
E. nana, Iodameba, E. coli and Giardia	1	3
E. nana and E. coli	2	2
E. nana, E. coli and Blastocystis	6	14
E. nana Trichomonas and Blastocystis	1	2
E. nana and E. histolytica	2	10
E. nana and unidentified motile ameba	1	1
Total occurrence of E. nana	64	131

The incidence of infection was 17.4 %.

Endamœba tenuis is one of the most frequently encountered amebæ of man but is usually not distinguished from *Endolimax nana* which it resembles in shape and staining qualities and to which it may be intimately related. Although its specific distinction is not widely accepted we are tentatively recognizing it and separating it from *E. nana* in this study. It was first described by Kuenen and Swellengrebel,[9] and has been confused with the smaller races of *E. histolytica*.[10] Its importance has been noted by Kofoid[11] and placed in the genus *Councilmania*. It is distinctly larger than *E. nana* and its nuclear structure is different with a smaller more centrally placed karyosome. Intermediate forms between the two types are lacking in our material and this constitutes our principal reason for classifying them separately. It must be admitted that differences of technique might be adequate to account for many distinctions in morphology. As experience is added, our distrust of purely morphologic criteria grows. Although *E. tenuis* was associated with *E. nana* in one-half of the cases we cannot accept this as evidence of genetic relationship because the same association is seen between *E. coli* and *E. nana*, or between Blastocystis and *E. nana*. The following table shows its association with other organisms:

TABLE 3.—INCIDENCE OF E. TENUIS.

	No. cases.	No. specimens.
E. tenuis alone	7	10
E. tenuis and Blastocystis	5	6
E. tenuis and E. nana	6	8
E. tenuis, E. nana and Blastocystis	4	9
E. tenuis, E. nana, Giardia and Blastocystis	2	12
E. tenuis, E. nana, Iodameba and Blastocystis	1	1
E. tenuis and Chilomastix	1	1
Total occurrence of E. tenuis	26	47

The incidence of infection was 7 %.

TABLE 4.—INCIDENCE OF IODAMŒBA BÜTSCHLII.

	No. cases.	No. specimens.
Iodamœba bütschlii alone	1	1
I. bütschlii and E. nana	1	3
I. bütschlii, E. coli, Giardia and E. nana	1	3
I. bütschlii, E. tenuis, E. nana and Blastocystis	1	1
Total occurrence of I. bütschlii	4	8

Incidence of infection 1.1%.

Dientamœba fragilis, a rare organism, was found in 2 specimens from 1 patient.

Giardia intestinalis was found 28 times in 9 different patients. It is the only commonly encountered flagellate which is conspicuous and readily found in stained smears. In none of our patients could symptoms be attributable to the infestation. One patient with a roentgenologic diagnosis of duodenitis had enormous numbers of the parasite in duodenal drainage material. Its normal habitat is in the duodenum, appearing in the stools in the encysted state usually, except in diarrhea when it is more likely to appear in the vegetative state. The following table shows its association with other intestinal protozoa:

TABLE 5.—INCIDENCE OF GIARDIA INTESTINALIS.

	No. cases.	No. specimens.
Giardia alone	2	2
Giardia and Blastocystis	5	16
Giardia, E. histolytica, E. nana and Blastocystis	1	7
Giardia, Iodameba, E. nana and E. coli	1	3
Total occurrence of Giardia	9	28

Incidence of infection: 2.4%.

Trichomonas hominis and *Chilomastix mesnili* are usually much more conspicuous in the fresh motile state than in stained material, where, if not numerous, they may be overlooked by the best observers. This report is based upon stained slides and therefore gives an apparent incidence of infection which is probably below the actual figure. They are usually more numerous in liquid stools, especially in diarrhea, but no etiologic significance has been demonstrated.

The flagella of *Trichomonas* and *Chilomastix* are not conspicuous by our method of staining, so that recognition must depend upon the finding of oval or pyriform bodies with inconspicuous nuclei and at least traces of the intracytoplasmic portion of the flagellar apparatus. Trichomonas is most readily confused with intestinal yeasts, especially if the staining be too dark. Chilomastix has a larger and more vesicular nucleus more anteriorly placed than in Trichomonas and showing portions of the cytostome with its stained

border. The axostyle and chromatic basal rod are often the only flagellar structures discernible in Trichomonas. The following table shows the association of Trichomonas with other protozoa:

TABLE 6.—INCIDENCE OF TRICHOMONAS HOMINIS.

	No. cases.	No. specimens.
Trichomonas hominis alone	1	1
T. hominis and Blastocystis	1	1
T. hominis, E. coli and Blastocystis	1	6
T. hominis, E. nana and Blastocystis	1	2
Total occurrence of T. hominis	4	10

Incidence of infection: 1.1%.

TABLE 7.—INCIDENCE OF CHILOMASTIX MESNILI.

	No. cases.	No. specimens.
Chilomastix mesnili alone	2	2
C. mesnili and Blastocystis	1	4
C. mesnili and E. tenuis	1	1
C. mesnili, E. coli and Blastocystis	1	1
Total occurrence of C. mesnili	5	8

Incidence of infection: 1.4%.

Blastocystis hominis, an ubiquitous organism, is of importance because of the fact that its pleomorphism permits it to mimic ameba cysts. Its actual systematic position has not been established, but it is perhaps more closely related to the fungi than to the protozoa. A full recognition of its range of variation is essential to the accurate diagnosis of intestinal protozoa. In fixed smears stained by the iron hematoxylin method it is seen as a spherical body ranging in size from that of the smallest to the largest ameba cysts. The essential feature upon which recognition depends is the double contoured or crescentic periphery when viewed in optical section. Between these two external membranes will be found small poorly defined masses of stained material. Most of the sphere consists of a large vacuole the contents of which may be the most striking element seen and which may vary in many ways. The contents of the vacuole may be mere hyalin material, may be clear or faintly reticular, or may be reticular and contain irregular masses of stained material deceptively resembling poorly stained nuclei of ameba cysts. In other instances the chromatic material may be more elongated or rod-like and resemble the chromatoidal bodies of ameba cysts. On other occasions the central mass will be dark and cloudy, perhaps containing granules of chromatin, and resembles an overstained ameba cyst. We suspect that technique or chemical factors in the stool affect the morphology of these bodies because there is a tendency for predominance of one or another of these types in any given preparation, and varying from time to time in the same patient. Although Blastocystis will scarcely confuse the expert, it is often most confusing to the novice. In unstained

material or after vital staining with eosin, Blastocystis has no striking resemblance to the parasitic protozoa, which is an advantage for this method.

The association of Blastocystis with other organisms may be seen by revision of the preceding tabulations. In addition, it occurred alone in 79 specimens from 64 patients. It was associated with other organisms in 147 specimens from 63 patients. The incidence of infection in this series is 34.5%.

Summary and Discussion. In a survey to determine the incidence of infestation with intestinal protozoa in patients entering the medical wards of a general hospital in Philadelphia during the winter of 1932–1933, the following results were obtained from a study of 535 fecal specimens from 368 patients:

TABLE 8.

	No. patients.	No. specimens.	Percentage incidence in total group.
Endamœba histolytica	4	23	1.1
Endamœba sp.?(probably motile moribund E. histolytica)	3	3	0.8
Endamœba coli	18	33	4.9
Endolimax nana	64	131	17.4
Endamœba tenuis	26	47	7.0
Iodamœba bütschlii	4	8	1.1
Dientamœba fragilis	1	2	0.3
Giardia intestinalis	9	28	2.4
Chilomastix mesnili	5	8	1.4
Trichomonas hominis	4	10	1.1
Blastocystis hominis	127	226	34.5
Negative for protozoa	197	308	53.8

Conclusions. These findings emphasize the importance of amebic infestation in Philadelphia and other cities in temperate climates. There are continually present an adequate number of infested individuals to serve as points of dissemination for future epidemics of amebic dysentery and chronic amebiasis. The practice of sanitation must take this fact into account and so control water supplies and food handling as to assure the destruction of the resistant amebic cysts along with the much more easily killed pathogenic bacteria. The recent epidemic in Chicago might be duplicated in Philadelphia if equal opportunities for dissemination should develop.

The diagnosis of amebic infestation is sufficiently difficult to lead us to emphasize further the fact that special experience, skill and facilities are essential to accurate reports from laboratories of clinical pathology.

Other amebæ, as well as motile mononuclear phagocytic body cells of large size, and Blastocystis are frequently confused with *E. histolytica*.

The clinical differentiation of amebiasis from chronic ulcerative colitis, malignancy of the colon, or neurogenic diarrheas, is not always possible.

Only careful, intelligent microscopic search of an adequate number of fecal specimens, properly collected, properly preserved and transported, and preferably aided by proctoscopy, can establish the diagnosis of acute chronic amebiasis.

The authors wish to express their gratitude to Dr. T. Grier Miller for the support and encouragement which made this study possible, and to Dr. Herbert Fox for revision of the manuscript and helpful suggestions.

REFERENCES.

1. Kofoid, C. A., Kornhauser, S. I., and Plate, J. T.: J. Am. Med. Assn., 1919, **72**, 1721.
2. Boeck, W. C., and Stiles, C. W.: Bull. No. 133, Hyg. Lab., Washington, 1923.
3. Meleney, H. E., Bishop, E. L., and Leathers, W. S.: Am. J. Hyg., 1932, **16**, 523.
4. Andrews, J., and Paulson, M.: Am. J. Med. Sci., 1931, **181**, 102.
5. Kofoid, C. A., and Swezy, O.: Am. J. Trop. Med., 1921, **1**, 41.
6. Craig, C. F.: J. Am. Med. Assn., 1932, **98**, 1615.
7. Magath, T. B., and Ward, C. B.: Am. J. Hyg., 1928, **8**, 840.
8. Kofoid, C. A., and Swezy, O.: Univ. Calif. Pub. Zoöl., 1923, **20**, 169.
9. Kuenen, W. A., and Swellengrebel, N. H.: Nederl. Tijdschr. v. Geneesk., 1917, **57**, 496 (quoted by Kofoid, 1928).
10. Nöller, W.: Die wichtigsten parasitischen Protozoen des Menschen und der Tiere, Berlin, Schoetz, 1922.
11. Kofoid, C. A.: Arch. Int. Med., 1928, **41**, 558.

THE AGE-INCIDENCE RELATIONS IN DIABETES MELLITUS.

By Gregory Pincus, Sc.D.,
ASSISTANT PROFESSOR OF GENERAL PHYSIOLOGY, HARVARD UNIVERSITY,

Elliott P. Joslin, M.D.,
CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; MEDICAL DIRECTOR OF THE GEORGE F. BAKER CLINIC, NEW ENGLAND DEACONESS HOSPITAL,

AND

Priscilla White, M.D.,
PHYSICIAN, NEW ENGLAND DEACONESS HOSPITAL, BOSTON, MASSACHUSETTS.

(From the Laboratory of General Physiology, Harvard University, and the George F. Baker Clinic at the New England Deaconess Hospital.)

A tabulation of the proportion of diabetics developing diabetes at various ages gives, of course, only the susceptibilities to diabetes of those who have lived long enough to be attacked by the disease. A true picture of the susceptibility to diabetes at various ages is given by the ratio of the number of persons developing the disease to the number exposed to it at these ages. Thus the rate of mortality from diabetes represents the susceptibility of persons to death from diabetes. There are numerous tabulations and discussions of diabetes death rates, but we know of no presentation of the rates of onset of diabetes. We propose, therefore, to present here certain calculations of the onset rates of diabetes mellitus, and to indicate briefly our conception of their significance.

Table 1 contains a summary of diabetes onset data collected between the years 1898 and 1933, and is based upon 9853 cases of true diabetes mellitus. In Table 2 we have made a similar tabulation of the mortalities recorded as due to diabetes in the state of Massachusetts for the years 1901 to 1932.* Derived onset rates (Table 3) are based upon the 1920 life tables for the U. S. registration area. The employment of any other pertinent life table gives substantially the same general result. For purposes of comparison we have also presented in Table 3 mortality rates calculated in exactly the same way as the onset rates were calculated.

TABLE 1.—THE AGE OF ONSET OF DIABETES MELLITUS (EXPERIENCE OF E. P. JOSLIN, 1898–1933).

	Total number of cases per decade.		Per cent appearing in each decade.	
Decade.	Males.	Females.	Males.	Females.
1 . .	230	232	4.96	4.45
2 . .	336	332	7.24	6.37
3 . .	444	317	9.57	6.08
4 . .	638	565	13.75	10.84
5 . .	1082	1197	23.32	22.96
6 . .	1122	1577	24.19	30.25
7 . .	633	822	13.65	15.76
8 . .	150	164	3.23	3.14
9 . .	4	8	0.09	0.15
Totals	4639	5214	100.00	100.00

TABLE 2.—DIABETES AS A CAUSE OF DEATH (MASSACHUSETTS 1901–1932).

	Total number of deaths per decade.		Per cent appearing in each decade.	
Decade.	Males.	Females.	Males.	Females.
1 . .	238	259	2.72	1.93
2 . .	409	397	4.68	2.94
3 . .	414	436	4.73	3.23
4 . .	543	539	6.21	3.99
5 . .	849	1076	9.71	7.97
6 . .	1746	2931	19.97	21.72
7 . .	2515	4420	28.76	32.75
8 . .	1618	2740	18.50	20.33
9 . .	412	694	4.72	5.14
Totals	8744	13496	100.00	100.00

The *method of calculating* may be briefly indicated here. The data for each decade of Columns 4 and 5 of Table 1 are taken as expressing the number of diabetics appearing in each decade out of 100 diabetics identified. Among the males, for example, out of 100 diabetics identified 4.96 are aged 0 to 9.9 years, 7.24 are 10 to 19.9 years old, etc. We can determine by graphic interpolation the number of diabetics for each year of life. Since what we want to know is the ratio of the number of diabetics observed to the number of persons "exposed" to the disease, we turn to the 1920 life tables which give the number of white persons alive in each year of life out of an original quota of 100,000 born alive. Thus, among males, this table tells us that out of 100,000 males born alive 91,567 survive to the end of the 1st year of life. Our incidence statistics state that by the end of the 1st year of life 0.43 male diabetics per 100 or 430 per 100,000 have had

* We are indebted to the Massachusetts Department of Public Health for the data employed.

diabetes onset. The ratio 430/91,567 gives us the onset rate for the first year of life among males. We have followed this procedure for each year of life up to age 90 assuming that diabetes onset does not occur after age 90. Columns 2 and 3 of Table 3 give *relative* onset rates. These are obtained by summating the rates for each year of life and setting the total equal to 100%, and then determining the proportion of this 100% in each decade. For purposes of comparison exactly the same procedure has been followed with the mortality data. We must stress the fact that these calculations are of necessity approximations both because of the method of calculation employed and because of the fact that the incidence data were collected over a period of years when changes in the average length of life and accuracy of diagnosis undoubtedly affected the age-incidence relations. This should be particularly obvious in the mortality data in which we lump data from the Naunyn, Allen and Banting eras. We believe, nonetheless, that our calculations do present sufficiently for our purpose the particular aspects of incidence relations stressed in the succeeding paragraphs.

TABLE 3.—RELATIVE ONSET AND MORTALITY RATES FOR DIABETES MELLITUS DERIVED FROM UNITED STATES LIFE TABLES FOR 1920.

	Relative onset rates.		Relative mortality rates.	
Decade.	Males.	Females.	Males.	Females.
1 . .	3.59	3.22	1.16	0.88
2 . .	5.41	4.74	2.06	1.37
3 . .	7.48	4.73	2.17	1.57
4 . .	11.48	9.06	3.05	2.08
5 . .	21.24	20.69	5.20	4.51
6 . .	24.86	30.48	12.22	13.93
7 . .	18.18	19.90	23.15	26.49
8 . .	7.12	6.23	25.42	26.26
9 . .	0.64	0.95	25.57	22.91
Totals	100.00	100.00	100.00	100.00

In Fig. 1 we have plotted the relative onset and mortality rates for males and females respectively. The onset rates represent the susceptibility to the *development* of diabetes in certain decades, the mortality rates represent the susceptibility to *dying* from diabetes in these decades.

Considering the onset rates alone the figures demonstrate that for both males and females the maximum susceptibility to the development of diabetes occurs in the 6th decade, and our more detailed figures show that age 51 among males and age 55 among females are the ages of maximum susceptibility. The susceptibility of males to the development of diabetes rises steadily to this maximum and thereafter declines. Females, however, have approximately equal chances of developing diabetes in the 2d and 3d decades. Furthermore, their chances of developing the disease are uniformly less than the chances of males until the 6th decade is reached, when their chances then and thereafter are greater than those for males.

To our minds the most significant aspect of these onset rates is the declining susceptibility in the later decades. This indicates

that diabetes is not an old-age disease.* It cannot be taken as a manifestation of senility. Its onset depends upon a complex of events (presumably endocrinal) which attain their maximum manifestation between the ages of 40 and 60. If we take the mortality rates of diabetes as the basis of an incidence study this situation would not be at all clear, for the mortality rates rise steadily until

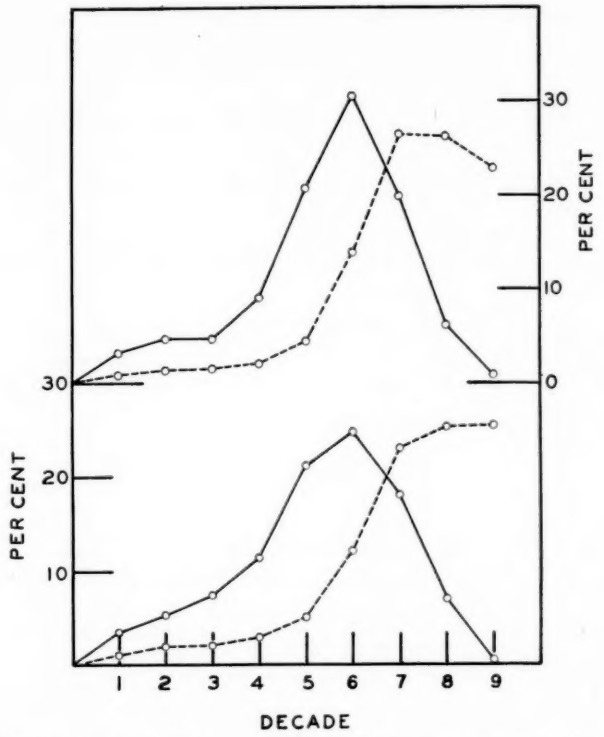


FIG. 1.—Relative onset and mortality rates of diabetes mellitus in the various decades of life. Full lines: onset rates; dashed lines: mortality rates. The upper curves represent the data for females, the lower curves those for males. Abscissa: the decades of life; ordinates: relative mortality in *per cent.*

the 9th decade (*cf.* Fig. 1), and even in this decade the slight decrease (noticeable only in females) is scarcely significant. The mortality rates imply that the older one grows the greater are the chances of dying from diabetes (*cf.* Mosenthal[1]), whereas the onset rates indicate that certainly after age 60 is reached the chances of developing diabetes decrease.

* It is interesting to note (1) that diabetics developing the disease after age 60 usually exhibit a mild diabetes, and (2) that the exact time of onset of diabetes in older patients is not as easily ascertainable as in younger diabetics, because the symptoms are less marked and develop insidiously.

The basis of this divergent set of expectations lies, of course, primarily in the length of time diabetes persists before it causes death. If we assume an average duration of the disease of some 10 to 12 years (and somewhat longer in females than in males) these onset and mortality statistics may be taken to corroborate each other. A comparison of the onset and mortality statistics indicates, furthermore, that the duration of the disease before it terminates in death will vary, depending upon the particular age at which it is developed. We feel that these data, however, do not justify any detailed investigation of this relation between age of onset and

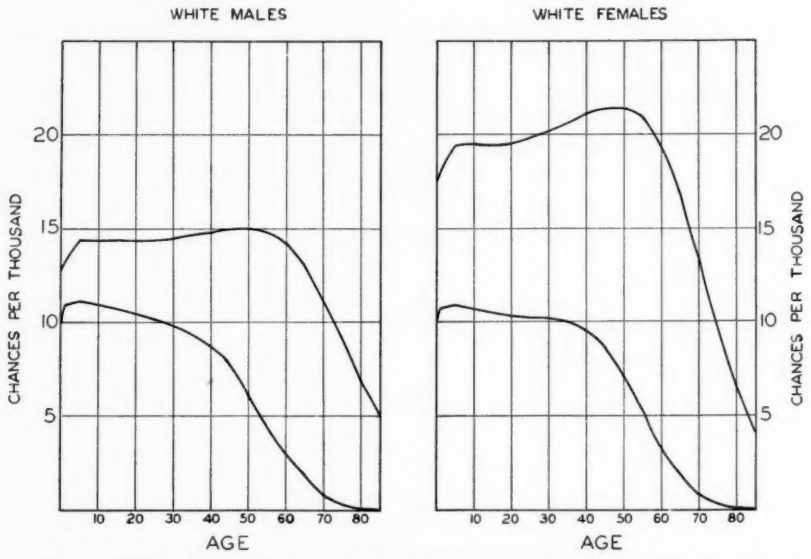


FIG. 2.—The chances of eventually dying from diabetes (upper curves) and of eventual diabetes onset (lower curves). Chances of death are absolute for the death registration states of 1920, and are calculated by the Metropolitan Life Insurance Company. The chances of diabetes onset are relative, *i. e.*, the chances at birth are arbitrarily taken as 10 per 1000 (see text), and are based on the 1920 life tables for the death registration states.

diabetes duration. In fact, the purpose of this communication is to draw attention only to the considerations immediately obvious when onset and mortality rates are compared. The finding, for example, that rising diabetes incidence with age occurs among fat diabetics in contrast to a constant incidence in thin persons (*cf.* Joslin[2]), would cause an alteration in the shapes of the incidence curves (Fig. 1), although the proportion of thin diabetics would have to be relatively large to alter the general result presented here.

The mortality and onset rates are age-specific and relate the susceptibilities at a given age. Calculations have been made of the chances of *eventually* dying of diabetes[3] (Fig. 2). We have made

similar calculations of the chances of eventually developing diabetes on the basis of our onset data. Since we have no absolute statistics of the number of persons developing diabetes we have arbitrarily set the chances at birth as 10 per 1000 and those obtained for all succeeding ages are relative to that arbitrary initial assumption. Since what we are interested in are the relative chances of *eventual* diabetes onset and *eventual* mortality from diabetes this procedure is entirely justifiable. Our comparison then deals with the slopes of the lines of Fig. 2, not with their absolute values. It will be seen at once that the mortality data indicate that the chances of eventual death from diabetes rise to a maximum at age 50 for both males and females, whereas the maximum chances of eventual onset are had at age 5. Furthermore, the chances of eventual death from diabetes begin to decline rapidly at about age 60 and a similar rapid decline in onset chances sets in at about age 40.

We wish to acknowledge the material assistance received from a fund created by Mr. and Mrs. Francis P. Garvan.

REFERENCES.

1. Mosenthal, H. O.: Bull. New York Acad. Med., 1933, **9**, 505.
2. Joslin, E. P.: Treatment of Diabetes Mellitus, 4th ed., Philadelphia, Lea & Febiger, 1928.
3. Metropolitan Life Insurance Company, Statistical Bulletin, April, 1933.

THE PRESENT STATUS OF THE DIAGNOSTIC INTRADERMAL TEST FOR HUMAN TRICHINIASIS.

By Richard D. Friedlander, M.D.,
ASSISTANT RESIDENT PHYSICIAN, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

Recently Kilduffe[1] reported the results of intradermal tests performed on 33 individuals recovered from trichiniasis following an outbreak of this disease in Atlantic City, N. J. He came to the conclusions that the demonstration of eosinophilia in human trichiniasis was not only technically simpler than the demonstration of the skin test, but also always feasible; whereas the skin test, requiring an antigen difficult to prepare, was feasible only when the antigen was available; and that the intradermal test in the study of human trichiniasis presents no practical advantages over the demonstration of eosinophilia.

It would appear that some recent publications on the use of serologic methods in diagnosing trichiniasis had not come to Kilduffe's attention, since, if these had been consulted, they would have given a different interpretation to his results. It is the purpose of the present communication to minimize any element of

confusion which might have been introduced by the paper under discussion, and also to review briefly the present status of the diagnostic intradermal test for trichiniasis.

In 1932 Augustine and Theiler[2] reported a critical study of the value of skin and precipitin tests as aids to diagnosis in this disease in which the skin reactions both in man and swine were described in detail and illustrated in color. The intradermal reaction in these hosts was found to be of the immediate type and was observed to occur within 5 to 15 min. after the injection of the antigen, fading of the reactions commencing during the first hour after the injection. On the other hand, the reaction in laboratory animals, guinea-pigs and rabbits, as described in the early work of Bachman,[3] was of the delayed type, being observed usually 24 hrs. after the injection of the extract. The course of the reaction in laboratory animals was found to bear no resemblance to that in man. Moreover these authors noted in their work that many persons were naturally hypersensitive to the antigen in concentrated dilutions, so that in order to rule out non-specific protein sensitivity they employed a 1 to 10,000 dilution of the antigen for routine use.

In 1933 McCoy, Miller and Friedlander[4] reported a study in which the results of skin tests performed on 88 individuals known to have had trichiniasis were tabulated. The antigen used in this work had been previously subjected to 539 control skin tests and in addition control tests were performed on 232 patients in Rochester, N. Y., 47 in San Francisco and 124 persons in southern Louisiana. The outstanding conclusions of this work were that about 90% of persons ill with trichiniasis will give a positive skin test to the trichinella antigen, provided the disease is sufficiently established. This period was found to be between 2 and 3 weeks after infection in the majority of instances. It was found, in addition, that positive reactions obtained with antigen dilutions of 1 to 10,000 or higher enhanced the specificity of the test and were of more definite diagnostic value than those obtained with lower dilutions. Under the same circumstances it was felt that a negative test would be of relatively greater value in ruling out the disease.*

Presumably not being conversant with this work, Kilduffe used an antigen in a dilution of 1 to 100, did not read his reactions for 24 hrs. after their execution, and employed Bachman's classification of degrees and type of reaction found in laboratory animals as a standard for human infection. His results, therefore, cannot be accepted as revealing the diagnostic value of the test.

Kilduffe is correct that the intradermal test has one disadvantage which does not apply to the demonstration of eosinophilia, providing the latter is present, namely, that the antigen is difficult to prepare

* Further confirmation of these observations have appeared in a more recent paper by Maternovska,[5] who concludes that the intradermal reaction in man, laboratory animals and swine is specific and diagnostic.

and hence to obtain. Nevertheless this is very different from demonstrating that the intradermal test does not have definite advantages over the demonstration of eosinophilia, when the degree of specificity of the test is considered. Moreover, it is well known that eosinophilia may be present in a large number of other parasitic and allergic conditions and, on the other hand, may be entirely absent in acute fulminating cases of trichiniasis terminating fatally, even when larvæ are demonstrable in the blood and spinal fluid.

Summary. Several years' experience of the author and his former associates, as well as that of Drs. Augustine and Theiler, with the intradermal test in hospitals in San Francisco, Rochester, New York and Boston, where trichiniasis not infrequently occurs, justify the conclusion that it is a valuable aid in the diagnosis of this disease.

REFERENCES.

1. Kilduffe, R. A.: Am. J. Med. Sci., **186**, 802, 1933.
2. Augustine, D. L., and Theiler, H.: Parasitology, **24**, 60, 1932.
3. Bachman, G. W.: J. Prevent. Med., **2**, 513, 1928.
4. McCoy, O. R., Miller, J. J., and Friedlander, R. D.: J. Immunol., **24**, 1, 1933.
5. Maternovska, I.: Zentralbl. f. Bakteriol., I. Abt., Orig., **129**, 284, 1933.

Errata.

We have been informed by the authors that in the March issue of the American Journal of the Medical Sciences, on page 378, Paragraph 2, Line 8, the sentence should read, "In over 6 per cent of the syphilitic group, the heart muscle was the seat of infarction."

In Table I. under "Syphilis of aorta," the number of cases of infarct of the heart should be "three" instead of "twelve."

BOOK REVIEWS AND NOTICES.

External Diseases of the Eye. By Donald T. Atkinson, M.D., Consulting Ophthalmologist to the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas, etc. Pp. 704; 479 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $7.50.

This textbook, dealing with those conditions of the eye which do not require elaborate equipment for diagnosis, covers a portion of ophthalmology in which there are no recent publications in English. The copious illustrations—all new as far as use in a textbook of ophthalmology are concerned—are mostly photographs of drawings or wax models prepared by the author and are almost diagrammatic in the clearness with which the pathologic features are delineated. Included in the appropriate sections are descriptions and illustrations of numerous ocular complications of leprosy.

The text deals with glaucoma, cataract and the ocular muscles, as well as in a strict sense the external eye. Operative treatment and technique occupies a prominent part of each section of the book and the experience and preferences of the author are presented.

The last two sections contain chapters on the hygiene of the eye and prescriptions used in the treatment of ocular conditions.

The volume is one which should be particularly useful to the general practitioner and to the student. The more experienced ophthalmologist, however, would prefer greater detail concerning the anatomy of the eye and pathology of the conditions described. W. F.

Diseases of the Skin. By Oliver S. Ormsby, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago, etc. With revision of the Histopathology in this edition by Clark Wylie Finnerud, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago, etc. Pp. 1288; 619 illustrations and 3 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $11.50.

"In order to incorporate new material and yet keep the book reasonable in size much reconstruction has been necessary. Thirty-six new diseases are described, 20 rewritten and the entire work brought up to date. Some of the more important new affections are: Tularemia, thromboangiitis obliterans, dermatomyositis and scleredema adultorum. The dermatologic literature has been carefully reviewed in order that this work may reflect its subject as completely as the limits of a single volume permit. As heretofore, articles have been selected on the various subjects which contain complete bibliography to date of publication, thus reducing the number of literature references. These will serve as a guide to the investigative student in working up any particular subject." (From author's Preface.)

Early Science in Oxford. By R. T. Gunther. Vol. IX. De Corde, by Richard Lower, London, 1669. With Introduction and Translation by K. J. Franklin. Pp. 220; illustrated. Oxford: For subscribers at University Press, 1932. Price, £1 1s.

This, the ninth of the author's contributions to his study of early science at Oxford, presents a facsimile and good translation of Lower's "epoch

making" (in the author's words) treatise on the heart. While many will perhaps recall the Lower's tubercle of student days, but few realize how important this work was in advancing the new knowledge of the heart and circulation, so gloriously inaugurated by Harvey a generation earlier. Lower's knowledge of the myocardial layers is a case in point. Biographic and bibliographic notices are useful additions, though even more of a background for the translation would have been welcome. E. K.

I REUMATISMI CRONICI. By DOTT. RICCARDO ARRIGONI. Pp. 344; illustrated. Pisa: Casa Editrice W. Giardini, 1933–XI. (Price not given.)

THE vast literature on chronic rheumatism is systematically and concisely reviewed and some original observations added with interpretations of clinical observations in the light of extensive recent experimental advances. All of the well known etiologic factors are discussed in some detail, and the variations in joint manifestations, not only in different individuals but also in the same individual at various periods in his life, are analyzed. The allergic factor is considered one of the most important recent contributions and the author believes that in the future studies of the allergic state will furnish the differential criteria between the various forms of rheumatism. A. C.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOLUME 9, MONOGRAPH 16, PART 1, INFLUENZA. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 640; 28 plates of illustrations, various charts and tables. Baltimore: The Williams & Wilkins Company, 1933. Price, $12.50.

PART I of this Monograph on Influenza deals especially with the "Part played by Pfeiffer's Bacillus, Streptococci, Pneumococci, etc., and the Virus Theory." It is, however, a monumental compilation of the literature (both foreign and American) dealing with history, epidemiology, symptomatology (differential diagnosis), mortality and bacteriology of the disease supplemented by personal observations.

The authors are conservative in their conclusions regarding the various bacteria thought at different times to be etiologic agents of the disease, stated, that "although there is much doubt as to whether or not Pfeiffer's bacillus is the primary cause of influenza; there is an almost unanimous agreement that it is the most important secondary invader, even more than the pneumococcus and the streptococcus, and that it is responsible for the great majority of the cases of fatal bronchopneumonia and many other complications. In these cases it occurs in enormous numbers and dominates the picture" (page 516). They feel that whatever the primary cause, "the disease very quickly becomes a symbiotic infection in which the bacteria play a most important and dangerous rôle" (page 568), although the evidence is "insufficient to prove or disprove any etiological relationship between B. pneumosintes and epidemic influenza" (page 590). They conclude that the most recent work is "consistent with the view that epidemic influenza in man is caused primarily by virus infection" (page 629), "but cannot accept the evidence, as at present presented, as definite proof that the filterable virus influenza has been cultivated;" (page 628.)

Their own contribution consists of the continued systematic study on a

standardized Crowe's medium of chocolate blood agar with photographic records of the cultures of the bacterial flora of the throat and sputa of the personnel of their research laboratory, at frequent intervals for the past 4 years. These "normal" findings were checked against cultures at the beginning of a catarrhal infection. Their results were reported in 1929, indicating that "normal" flora is 90% streptococcal, varying every week, even in health. They found that a streptococcus caused an epidemic of influenza in 1927 and that one of a different type was occurring in large numbers in the epidemic of 1929. From these findings they "suggest, therefore, that the so-called influenza epidemic may be due to virulent streptococcal infections of the respiratory tract and that these streptococcal infections may vary with the various epidemics" (page 561).

The type is clear, photographic plates are excellent and the entire monograph forms a fitting companion to the previously published volumes.

J. C.

THE CORTICAL LOCALISATION OF CEREBRAL FUNCTION. By PROFESSOR J. SHAW BOLTON, M.D., D.Sc., F.R.C.P., The Henderson Trust Lectures, No. XII. Pp. 23; 23 illustrations. Edinburgh: Oliver and Boyd, 1933. Price, 6d.

THIS lecture is an elaboration of an article published by the author about 30 years ago (Further Advances in Physiology). It gives an excellent summary of the comparative anatomy of the cerebral cortex and of the light thrown upon its function by psychiatry and pathology. It concludes with an interesting review of the important recent paper by Fulton, Jacobsen and Kennard in *Brain*, vol. **55**, 1932, on the function of the premotor area.

G. McC.

BACTERIOLOGY FOR MEDICAL STUDENTS AND PRACTITIONERS. By A. D. GARDNER, D.M., F.R.C.S., Fellow of University College; Oxford Member of Research Staff, Medical Research Council. Pp. 276; 31 illustrations, 27 tables. New York: Oxford University Press, 1933. Price, $2.25.

"THE chief aim of this book is to present shortly, readably, and relevantly as much of the vast subject of bacteriology as a medical student or practitioner needs to know; leaving details of technique to a practical course, and emphasizing the wider biological relations of microbe and man." Adherence to this aim, as set forth in the author's preface, enabled this huge subject to be treated in a small volume. Pathogenic bacteria, fungi and protozoa, as well as filterable viruses, bacteriophage and immunology, have been considered. The material present—of course, only the bare essentials—is up to date. It might be found a little too elementary for present-day medical students, but it should be helpful to practitioners who have been unable to keep up with the recent advances in bacteriology and immunology. It should certainly prove to be highly interesting to laymen.

H. M.

THE GENIUS OF LOUIS PASTEUR. By PIERS COMPTON. Pp. 361, illustrated. New York: The Macmillan Company, 1932. Price, $4.50.

LIKE his subject, the author of this appreciative "life" has keen regard for the human side of his subject matter. He sees Pasteur as the scientist, to be sure, who "in the interests of his dedication, was forced to live somewhat apart," yet as "one who worked solely for the human element." Admitting that this feature lends warmth to the picture and even can be said to have helped Pasteur toward his great discoveries, it should also be recognized, as the author has apparently failed to do, both that it at times

worked to the detriment of the finished product and also that similar intensities focussed too sharply on one geographical area have marred the contributions to our civilization of other great Frenchmen. The "grandeur of science" must be mingled by Pasteur with "the grandeur of France," on the bright side exemplified by his willingness to give the hydrophobia treatment to Louise Pelletier, a hopeless case (p. 313), on the narrower side by his attitude during the Franco-Prussian war. At the point of death in his paralytic attack (1868), he was heard to murmur, "I am sorry to die, I wanted to do so much more for my country." What he lived to do is known to all, and the appreciation of the French people is shown by the popular vote, easily placing him as the greatest Frenchman of all time. This vivid depiction of an heroic personality should give pleasure to many who perhaps are unfamiliar with Vallery-Radot's fascinating "Life" and with the extensive biographical material that already exists in English. E. K.

MEDICINE IN VIRGINIA IN THE NINETEENTH CENTURY. By WYNDHAM B. BLANTON, M.D. Pp. 466; illustrated. Richmond, Va.: Garrett & Massie, Inc., 1933. Price, $7.50.

This, the third volume covering the three centuries of Virginia medical history, completes the task undertaken by the author for the sponsors of the work, the Medical Society of Virginia. What it lacks in the picturesqueness of the pioneer and colonial figures it compensates for in the importance of the accomplished work that is portrayed. The story of the rise of 9 medical colleges in a half century, and their later consolidations, typifies current conditions in this country. In the first half century one is surprised to learn the numbers of Virginians who graduated from Northern institutions: in 1819, from the P. & S., 9 from Virginia and 15 from New York; from Pennsylvania, 37 Virginians, 21 Pennsylvanians. In 1841, there were 36 Virginia graduates in a Pennsylvania class of 109; at Jefferson 12 out of 59, and so on. While the ground covered by the 18 chapters of this invaluable reference book is much too extensive for notice here, we note with special interest the chapters on medical societies, journals, the specialties, cults, hospitals and epidemics. E. K.

NEW BOOKS.

Obstetric Medicine. Edited by FRED L. ADAIR, M.A., M.D., F.A.C.S., Mary Campau Ryerson Professor of Obstetrics and Gynecology, etc., and EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Rush Medical College of the University of Chicago, etc. Pp. 743; 24 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1934. Price, $8.00.

Lehrbuch der Inneren Medizin, Vols. 1 and 2. By G. v. BERGMANN, and others. Pp.: Vol. 1, 914, Vol. 2, 794; illustrations: Vol. 1, 144, Vol. 2, 146. Berlin: Julius Springer, 1934. Price, Rm. 45 and 49.80.

Diseases Peculiar to Civilized Man. By GEORGE CRILE, M.D. Edited by AMY ROWLAND. Pp. 427; 41 illustrations. New York: The Macmillan Company, 1934. Price, $5.00.

Practical Methods in Biochemistry. By FREDERICK C. KOCH, Professor of Physiological Chemistry, University of Chicago. Pp. 282; 17 illustrations. Baltimore: William Wood & Co., 1934. Price, $2.25.

Industrial Toxicology. By ALICE HAMILTON, M.D. Pp. 329. New York: Harper & Brothers, 1934. Price, $3.00.

I know just the thing for that! By J. F. MONTAGUE, M.D., Medical Director, New York Intestinal Sanitarium, etc. Pp. 265. New York: The John Day Company, 1934. Price, $2.00.

Another attempt to tell the layman that when ill he should seek the advice of a doctor and avoid that of his friends.

The Bristol Medico-Chirurgical Journal. Combined Index for Volumes 1 to 50, 1883–1933, Inclusive. Pp. 72. Bristol: J. W. Arrowsmith, Ltd., 1934. Price, 3/–net.

Modern Drug Encyclopedia and Therapeutic Guide. By JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Consulting Physician, Manhattan General Hospital, etc. Pp. 1393. New York: Paul B. Hoeber, Inc., 1934. Price, $7.50.

Atlas of Pathological Anatomy, Volume 1. Compiled by E. K. MARTIN, M.S., F.R.C.S. Pp. 489, mostly illustrations, many colored. Baltimore: William Wood & Co., 1933. Price, $15.00.

The Cyclopedia of Medicine, Vol. 9. By GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D.; CONRAD BERENS, M.D.; P. BROOKE BLAND, M.D.; FRANCIS L. LEDERER, B.S., M.D.; A. GRAEME MITCHELL, M.D. Pp. 1166; illustrated with half-tone and line engravings, also full page color plates. Philadelphia: F. A. Davis Company, 1934.

The Chemistry of the Hormones. By BENJAMIN HARROW, PH.D., Associate Professor of Chemistry, The City College, College of the City of New York, and CARL P. SHERWIN, D.SC., M.D., DR.P.H., on the staff of St. Vincent's and French Hospitals, New York City. Pp. 227. Baltimore: The Williams & Wilkins Company, 1934. Price, $2.50.

The Medicolegal Necropsy. A Symposium held at the Twelfth Annual Convention of the American Society of Clinical Pathologists at Milwaukee, Wisconsin, June 9, 1933. Edited for the Society by THOMAS B. MAGATH. Pp. 167; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, $2.50.

NEW EDITIONS.

Diseases of the Skin. By OLIVER S. ORMSBY, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago, etc. With revision of the Histopathology in this edition by CLARK WYLIE FINNERUD, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago, etc. Pp. 1288; 619 illustrations and 3 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $11.50. (Review page 124.)

Chronic Nasal Sinusitis and Its Relation to General Medicine. By PATRICK WATSON-WILLIAMS, Honorary Consulting Surgeon in Diseases of the Ear, Nose and Throat, British Royal Infirmary, etc. With a Foreword by SIR HUMPHRY DAVY ROLLESTON, BART, G.C.V.O., K.C.B., Physician Extraordinary to H. M. the King, Emeritus Regius Professor of Physics, Cambridge. Pp. 262; 123 illustrations. Second edition. Baltimore: William Wood & Co., 1933. Price, $5.00.

Bergey's Manual of Determinative Bacteriology. By DAVID H. BERGEY, formerly of the University of Pennsylvania, Philadelphia, assisted by a Committee of the Society of American Bacteriologists. With an Index by ROBERT S. BREED, New York Agricultural Experiment Station. Pp. 664. Fourth edition. Baltimore: The Williams & Wilkins Company, 1934. Price, $6.00.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

PULSE WAVE VELOCITY.

THE increased importance year by year of degenerative cardiovascular disease, portrayed strikingly in our mortality statistics, has renewed with vigor in the past decade the pursuit of studies in arterial function. These studies in a large part hinge upon a study of arterial elasticity, the ability of an artery to stretch a certain amount with a given change in pressure, for arterial elasticity is a measure of arterial efficiency. An index of such efficiency is desirable as a functional test by which the normal and abnormal arterial state may be detected. Measurement of the velocity of the pulse wave has been practically the only method of measurement of this function in significant segments of arteries for the past 50 years.

The evolution of apparatus for the measurement of the velocity of the pulse wave, thought to have reached its height in the discard of ponderable mechanical levers by O. Frank, in the past decade has continued to advance with the introduction of electrical recording units. Bramwell, Hill and McSwiney[1] describe and use the hot-wire sphygmograph. This instrument is based on the principle that a current of air, passing over a hot platinum wire, cools the wire and changes its resistance. Puffs of air from a recording cuff over an artery pass through a tube containing a hot platinum wire, changing its resistance. With the aid of a Wheatstone bridge this change in resistance produces a current which flows through the string of an Einthoven galvanometer, thus graphically recording the pulsation. Because of the relatively enormous surface of the small platinum wire (3600 sq. cm. per cc. of metal) cooling takes place at a rapid rate and very small puffs of air are sufficient to cause a rapid change in resistance. Bramwell[2] states that lag and inertia are entirely abolished and commencement of upstroke is clearly defined. However, the method is cumbersome, produces a diphasic response, and does not permit the study of wave form.

Turner[3] has described a superior recording unit. Carbon grain microphones are placed over the arteries to be studied. As the pulse wave passes under the microphone the resistance in the microphone is changed, varying the current flowing through the instrument. The current passes through a string galvanometer, recording beautiful sphygmographic tracings. This technique possesses all the advantages claimed by the hot-wire method with none of the disadvantages.

Furthermore, the lag entailed in the conduction of air through tubing is entirely eliminated.

More recently Mantoba[4] has described a recording system consisting of a condensor and an electric amplifier with the 3-electrode vacuum tube. "The movement of the pulse is conducted to the variable condensor, and this tiny movement causes a great change in the direct current of the detector, and this is photographed with the oscillograph." Excellent sphygmograms are obtained and measurement of pulse wave velocity could be done easily by this technique.

The determination of pulse wavé velocity as an indication of a diseased arterial state depends necessarily on a knowledge of the normal variation. However, investigations on pulse wave velocity in the healthy individual have not disclosed as yet limits of normal which are generally accepted. The variety of methods used, from the early ponderable lever instruments through the segment capsule of Frank to the newer electrical instruments, have given a wide variation in the figures for normal range. We shall consider here only the results of the more modern technique.

Most workers do agree that pulse wave velocity increases with age. Bramwell, Hill and McSwiney,[1] in 74 subjects from 4 to 84 years of age, obtained pulse wave velocities from 4.7 to 8.6 meters per second, showing a definite relationship between age and velocity, the velocity increasing with the age. The greatest deviation from the mean curve for different ages was less than 1 meter per second. Since pulse wave velocity is a measure of arterial elasticity it can be seen from these data that arterial elasticity diminishes with advancing age.

Moens' original formula[5] is $V = \sqrt{\frac{E\,c}{2\,p\,r}}$, in which V is the pulse wave velocity E the coefficient of elasticity of the artery for lateral expansion, c the thickness of the arterial wall, r the radius of the artery in diastole and p the density of blood. This equation has little practical value because V, c and r are all unknowns and c and r are difficult to determine. Because of this unwieldy formula Bramwell and Hill[6] derived a formula which by conversion to percentage values finally gave the following relationships:

$$V = \frac{3.57}{\sqrt{\%\text{ increase in volume per mm. of Hg increase in pressure}}}$$

With this formula only one observation (V) is required from which one can calculate the extensibility of the arterial segment studied.

Calculation of the elasticity of the arteries for different age groups by this formula showed that the value is practically halved from 10 to 60 years, adequately explaining the widening of pulse pressure and increase in systolic pressure with age.

Beyerholm[7] obtained similar results in variation with age, the pulse wave velocity varying from 4.06 to 8.17 meters per second in an age group from $1\frac{1}{2}$ to 78 years. The individual values, however, are slightly higher than those of Bramwell and his co-workers. Hafkesbring and Ashman,[13] using an optical method, obtained a range from 5.8 to 10.3 meters per second in 90 normal subjects, results which are still somewhat higher than those of Beyerholm.

In all the determinations the diagnosis of a normal individual or one without a certain degree of arteriosclerosis after the sixth decade of life is doubtful.

The relationship of arterial caliber to pulse wave velocity has been a little studied although significant factor. It is only recently that convincing proof of the relationship put forward in Moens' formula 56 years ago has been demonstrated satisfactorily in the intact artery. Bazett and Dreyer[8] showed that the pulse wave velocity in the brachial and radial arteries was faster and more variable than in the aorta and femoral. Fulton and McSwiney[9] confirm these findings. The study of the effect of arterial caliber as a single variable upon pulse wave velocity in circulatory schema has not been done satisfactorily. The interrelationship of arterial caliber and arterial tone also remains unsolved.

In contrast to the few investigations on arterial caliber the effect of diastolic blood pressure upon the elasticity of the arterial wall has received much consideration. The thesis that increased blood pressure stretches the artery to a more inelastic state, in this way increasing the pulse wave velocity, has been the explanation of variations in pulse wave velocity with changes in diastolic blood pressure. Bramwell, Downing and Hill[10] have determined the effect of blood pressure on pulse wave velocity in the isolated human artery by the hot-wire technique. Mercury was used as a medium to replace blood because it gives a time interval 3.58 times as long and is much more accurately measurable. By this technique a definite close relationship between blood pressure and pulse wave velocity was demonstrated, although it must be admitted that the results upon an extirpated artery, stripped of its anatomic and physiologic relationships to other tissues in the body, cannot be applied wholly to the intact animal.

Demonstration of a similar relationship between blood pressure and pulse wave velocity in the intact artery in the human has not been uniformly successful. Bazett and Dreyer,[8] Bramwell, Hill and McSwiney,[1] Hickson and McSwiney[11] state that pulse wave velocity in normal individuals varies with diastolic pressure. Sands[12] confirms these results. Others, however, are not in full accord. Fulton and McSwiney[9] were unable to establish a relationship between arterial blood pressure and pulse wave velocity. The results of Hafkesbring and Ashman[13] are interesting in that they obtained a significant correlation among women but not among men. Sands,[12] in 14 cases of aortic regurgitation, found no significant change in the range of pulse wave velocity and no correlation with the lowered diastolic blood pressure.

While blood pressure, arterial size, and age have long been considered the important factors affecting the pulse wave velocity in the normal, failure of various observers to confirm results of others suggest that some other factor is operative. In recent years another most important factor has gradually taken its place as an important variable affecting pulse wave velocity. This factor is arterial tone, which affects arterial elasticity presumably through its effect on smooth muscle. I have already referred to the variable pulse wave velocity obtained by Bazett and Dreyer in the peripheral muscular arteries. They suggested the possibility that local conditions of vasoconstriction or dilatation were operative in these determinations. Hemingway,

McSwiney and Allison[14] determined the pulse wave velocity over segments of brachial artery in which they had varied the effective pressure upon the arterial wall by means of a wide armlet under variable pressure. Their calculation of arterial elasticity from these experiments led them to a classification of arteries into hyperextensible, normal and hypoextensible types. This classification of arteries and divergence of their results from the age incidence curve led McSwiney and his associates to believe that smooth muscle tone influenced arterial extensibility. Presumably, they state, this may be influenced by nervous mechanisms through the vasomotor center so that structures with the same histologic appearance may differ widely in their activity. It may be asked, if determinations were made repeatedly at different sittings on these same individuals, whether the same person may at one time fall into the hyperextensible, at another into the hypoextensible or normal groups? This question is not as yet answered.

As long ago as 1917 Dawson[15] presented conclusive proof of changes in arterial elasticity independent of blood pressure. He varied the blood pressure in dogs by nerve stimulation and noted that "the curve of elasticity would, after rising steadily in correspondence with the rise in pressure, suddenly fall or begin to oscillate up and down. Consequently, if one would determine the rate of transmission the pulse wave for a pressure of 60 mm. he might find 10 minutes later that this value corresponded to an entirely different pressure." He concludes that insofar as the pulse wave velocity may be regarded as an index of arterial elasticity it indicates that in the living animal the coefficient of elasticity is irregularly variable, and it is suggested that this variability may be due to changes in the tonus of the vascular walls.

Reuterwall[16] plotted extension curves of extirpated arteries in tests made in rapid succession. Differences were found between successive curves. Treating the same arteries with adrenalin modified the shape of the curves. The arteries used were of the muscular type.

More recently Turner and Sodeman[17] have done repeated determinations of pulse wave velocity in the same individuals to determine spontaneous fluctuations. Their data show that pulse wave velocity may vary widely in the same individual from time to time, the determinations often being in what has been considered the absolutely abnormal range only to return later to the so-called normal range. These results not only change the concept of normal range of pulse wave velocity but demonstrate clearly frequent changes in arterial elasticity which they suggest are changes in smooth muscle tone dependent upon vasomotor responses.

The use of pulse wave velocity as an indication of disease has been applied chiefly to arteriosclerosis, aneurysm and hypertension. The relationship of pulse wave velocity to hypertension is usually explained upon the basis of stretch of the arterial wall to a less elastic state, thus causing an increase in pulse wave velocity. Beyerholm,[7] from his investigations, concludes that blood pressure and pulse wave velocity are not directly proportionate in their changes. Turner and Herrmann[18] noted that, in some individuals with hypertension, pulse wave velocity actually increased when blood pressure was lowered with nitrites. These results seem to indicate that influences other than simple stretching, as in a rubber tube, are operative in hypertension.

The thickness of the arterial wall was indicated by Moens in his

formula as a factor influencing pulse wave velocity. In the normal individual this factor is of minor importance. Arteriosclerosis, by its increase in the thickness of the arterial wall, as well as by the changes in the wall which reduce its elasticity, with a resultant more rigid tube, would lead to an increase in pulse wave velocity. Bramwell and Hill[19] advocate the use in clinical medicine of pulse wave velocity determinations as direct objective evidence in the diagnosis of arteriosclerosis and aneurysm. In the light of investigations of others, however, their suggestions seem premature. Increase in pulse wave velocity is not a constant finding in arteriosclerosis. Sands[12] says "that from a series of 30 cases of arteriosclerosis in some instances the velocity of the pulse wave is increased and in others decreased." She found in circulatory schema that tortuosity slowed the velocity and believes she can explain the slow velocities on these irregularities of lumen and tortuosity great enough to overcome the lessened expansibility. Measurements of tortuous arteries are also inaccurate, for the tortuosity cannot be measured in the intact individual. Beyerholm,[20] in 26 individuals, 25 of whom had arteriosclerosis demonstrable by roentgenography, obtained values averaging 7.52 meters per second, a value a little less than the average for individuals of more than 60 years of age. He does not consider winding of the artery, which he has measured in some instances by dissection postmortem, sufficient to account for the discrepancy between the general conception and his results and states he has not made a deeper investigation of the problem. It can be seen, therefore, that pulse wave velocity as an objective indication of arteriosclerosis is not infallible. The results of Turner and Sodeman, together with the remaining evidence that changes in arterial tone are important in varying arterial elasticity, indicate that pulse wave velocity alone when it is elevated cannot be considered as evidence of organic changes causing increased arterial rigidity, and that temporary or transient variations in arterial tone must be ruled out. Until an adequate method of distinguishing these two factors is forthcoming pulse wave velocity alone, when increased, will be of little use in diagnosis of arteriosclerosis. Furthermore, since demonstrable arteriosclerosis may be present when pulse wave velocity is in normal range, low pulse wave velocity does not eliminate the possibility of arteriosclerosis being present.

Interpretation of low pulse wave velocity in arteriosclerosis has not as yet been attempted by workers in this field further than we have indicated. One must assume that all sclerotic arteries have not lost their elasticity. Arterial tone response to vasomotor stimulation must be investigated. Plesch[21] has helped open the way to such studies in his consideration of arterial tone. He considers the primary cause of arteriosclerosis a weakening of the muscular and elastic elements of the walls of the bloodvessels. If the weakened bloodvessels are unable to offer sufficient resistance to the blood pressure they become stretched and dilated. Whether or not this is the true situation, Plesch's work has stimulated the study of arterial tone. He sets for arguments to support his views which, although not convincing in themselves, are supported by oscillometric tracings.

W. A. S.

REFERENCES.

1. Bramwell, J. C., Hill, A. C., and McSwiney, B. A.: Heart, **10**, 233, 1923.
2. Bramwell, J. C., in Cowdry's Arteriosclerosis, New York, Macmillan Company, p. 82, 1933.
3. Turner, R. H.: Bull. Johns Hopkins Hosp., **43**, 1, 1928.
4. Mantoba, K.: Acta scholæ med., **14**, 240, 1932.
5. Moens, A. J.: Die Pulskurve, Leiden, 1878.
6. Bramwell, J. C., and Hill, A. C.: Proc. Roy. Soc. Med., **93** *B*, 298, 1922.
7. Beyerholm, O.: Acta med. Scandinav., **67**, 203, 1927.
8. Bazett, H. C., and Dreyer, N. B.: Am. J. Physiol., **63**, 94, 1922.
9. Fulton, J. S., and McSwiney, B. A.: J. Physiol., **69**, 386, 1930.
10. Bramwell, J. C., Downing, A. C., and Hill, A. C.: Heart, **10**, 289, 1923.
11. Hickson, S. K., and McSwiney, B. A.: J. Physiol., **59**, 217, 1924–1925.
12. Sands, J.: Am. J. Physiol., **71**, 519, 1924–1925.
13. Hafkesbring, R., and Ashman, R.: Ibid., **100**, 89, 1932.
14. Hemingway, A., McSwiney, B. A., and Allison, P. R.: Quart. J. Med., **21**, 489, 1928.
15. Dawson, P. M.: Am. J. Physiol., **62**, 613, 1917.
16. Reuterwall, O. P.: Acta med. Scandinav., Suppl., **2**, 1, 1921.
17. Turner, R. H., and Sodeman, W. A.: Proc. Soc. Exp. Biol. and Med., **31**, 831, 1934.
18. Turner, R. H., and Herrmann, G. R.: J. Clin. Invest., **4**, 430, 1927.
19. Bramwell, J. C., and Hill, A. V.: Lancet, **1**, 891, 1922.
20. Beyerholm, O.: Acta med. Scandinav., **67**, 323, 1927.
21. Plesch, J.: Lancet, **1**, 385, 1932.

PEDIATRICS

UNDER THE CHARGE OF

ALVIN E. SIEGEL, M.D.,

MACON, GEORGIA.

CALCIUM METABOLISM AND FACTORS INFLUENCING ITS PHYSIOLOGIC AND PATHOLOGIC VARIATION.

TETANY and spasmophilia have been recognized for years and the relation of parathyroid extirpation to the development of surgical tetany is so well established that preservation of parathyroid tissue in thyroidectomy is an essential responsibility of the surgeon. However, more attention has been attracted to the problem of calcium in the human mechanism during the last decade to the extent that a greater knowledge of its importance in maintaining a physiologic balance has been developed. This development has explained some of the conditions which before were classed from the etiologic standpoint as idiopathic. Among these conditions are tetany and spasmophilia. This subject may be said to be in a state of flux, and an attempt to review the literature may result in a certain amount of confusion; but because the evidence shows that calcium is a most important factor in the normal growth, development and wellbeing, especially in children, this presentation is offered.

Brown and Tisdall[1] state that there are at least 10 inorganic elements which are absolutely essential for life, namely, sodium, potassium, calcium, magnesium, phosphorus, chlorin, sulphur, iodin, iron and copper. "From the standpoint of the practising physician, we are

fortunate in having to watch the supply of only 3 of these elements, because any reasonable diet will furnish the other 7 elements in adequate amounts. The supply of the 3 elements, calcium, iron and iodin, however, should not be left to chance. Although calcium is the fourth most widely distributed element in the earth's crust, its occurrence in foods is quite limited. Our 2 chief sources of calcium are milk and leafy vegetables. As regards the child's diet, it may be stated that it is absolutely impossible to furnish an adequate amount of calcium unless liberal amounts of milk are given. This can be demonstrated readily by the following facts: A diet comparable to that found in many uninformed families composed of rolled oats and bread and butter for breakfast; beef, potatoes, carrots, cabbage and rice for dinner; potatoes, bread and butter, and honey or jam for supper, with 4 ounces of fluid milk to go on the rolled oats and rice—supplies only 0.3 gm. of calcium. Yet the average 10-year-old child requires approximately 1 gm. of calcium each day. The additional 0.7 gm. of calcium required can be furnished by 1 pint of milk per day, or a total milk intake of 24 ounces per day. If all of the milk is omitted, the amount of calcium furnished by the remaining portions of the diet is reduced to the absurdly low figure of 0.17 gm. It is thus evident that we depend mostly on milk to supply the large calcium needs of the growing child."

Daniels, Hutton, *et al.*[2] studied the relation of the ingestion of milk to calcium metabolism in children. As regards their results they comment in part as follows: "The amount of calcium that a child retains at any given time would seem to be a measure of his physiologic needs at that particular moment, provided enough is available. Single studies cannot determine how much calcium a child of a given age should retain. Balance studies should be made with the same children over a considerable length of time until one can be reasonably sure that they are physiologically full. It seems probable that diets which seemingly have resulted in low retentions have done so, not necessarily because the diets were too low in the given constituent, but because the child being studied needed less and, therefore, took from the amount offered only what he needed. This sometimes has been little, sometimes more. From the results herein reported, it seems clear that 1 pint of milk, when included in a diet which supplies approximately 23% of its calcium from other sources, will supply enough calcium for normal children of the ages studied when a sufficient amount of vitamin D or sunshine is allowed. Whether sufficient calcium will be obtained from diets containing 1 pint of milk when less calcium is given from other sources remains to be determined. Studies of diets which include lower levels of calcium and protein are now in progress." In summarizing their entire work they say: "Retentions of calcium, phosphorus and nitrogen have been determined in children receiving diets differing chiefly in the amounts of calcium, which was furnished by 1 pint and 1 quart of milk respectively. Although wide variation was found to exist in the amounts of these essential constituents retained by different children of approximately the same ages and by the same children under varying conditions of diet and of vitamin D, the results indicate that 1 pint of milk will supply sufficient calcium for the normal child between 3 and 5 years of age, provided the diet furnishes enough protein, phosphorus and vitamins from other sources. The marked

differences in the amounts of the various constituents of growth retained by the same children under varying conditions appear to be due to the physiologic conditions of the children at the time of the study and to their potentialities of growth. Those who had been previously well nourished retained more of the constituents of growth than did those who had been well fed. Normal children between 3 and 5 years were found to retain from 3 to 10 mg. of calcium, from 6 to 8 mg. of phosphorus and from 34 to 90 mg. of nitrogen per kg. It is suggested that the high retentions reported in previous investigations may have been due to the fact that the children under observation were more or less depleted in the substances studied."

Jeans and Stearns,[3] in reference to the retention of calcium and the development of bone on diets of evaporated milk, write: "The retention of calcium by the different infants and by the same infants at different periods showed considerable variation, but in general was high. In those periods in which there were definite symptoms of overfeeding (increased frequency of stools), the retention of calcium was decreased. Lowered retentions were observed also after apparent recovery from the infection. During the latter period the infants suffered from the lack of appetite. The serum of each infant was analyzed for calcium and inorganic phosphorus at intervals during the study. The values for calcium ranged between 10.2 and 12.1 mg. per 100 cc. The inorganic phosphorus values were higher than is often reported as normal, varying (with one exception) from 5.2 to 7.3 mg. per 100 cc. These high phosphate values have been observed for several successive years in this clinic in well children given a high intake of calcium and phosphorus, together with cod liver oil. . . . A study of the rate of ossification was undertaken by Miss Idell Pyle, of the Child Welfare Research Station of this university. (University of Iowa.) The average rate of ossification for the group of babies given evaporated milk was definitely above the average for Iowa infants. None of the infants was below the Iowa average; the 2 largest infants were usually within the Iowa average range, sometimes having an increased rate, and the others of the group were well above the Iowa average in the rate of ossification of carpal areas. An increased rate of deposition of minerals in bone and an increased rate of skeletal growth of the infants are indicated by the high mineral retentions, early carpal ossification, rapid growth in length and the entire absence of clinical or chemical evidence of rickets. The same factors offer abundant evidence that the amount of calcium retained from evaporated milk feedings, when these are accompanied by the dietary additions used with these infants, is amply sufficient to provide for excellent growth and development of bone. This finding is perhaps of particular interest in view of the retention of calcium observed in infants on pasteurized milk and is in line with the observations of Willard and Blunt, and of Kramer, Latzke and Shaw. Willard and Blunt found that evaporated milk is slightly superior to pasteurized milk as a source of calcium, phosphorus and nitrogen for children. Kramer, Latzke and Shaw observe that pasteurized milk gives less favorable calcium balance than evaporated or fresh milk . . . ."

Stearns[4] summarizes his results as follows: "The excretion and retention of nitrogen, calcium and phosphorus of an infant fed milk and various soy bean preparations have been determined. The rela-

tive proportions of nitrogen, calcium and phosphorus ingested differed with the diets. An increase in the relative intake of nitrogen and calcium, as compared to the phosphorus intake, resulted in an insufficient retention of phosphorus. Under these conditions the urinary excretion of calcium was tremendously increased, and the urinary phosphorus markedly decreased. The excessive excretion of calcium in urine noted with two of the diets is interpreted as evidence of an absorption of calcium greatly in excess of the amount which can be deposited in bone with the limited quantity of phosphorus available. The marked alteration in urinary secretion of phosphate was without apparent effect on the excretion of sulphate and chlorid in urine. Excessive excretion of calcium in the urine was accompanied by a shift in the mode of excretion of the other bases, decreasing the excretion in urine and increasing the fecal excretion. The altered calcium metabolism does not seem to affect the retention of fixed bases other than calcium. The substitution of dicalcium phosphate for calcium carbonate in the soy bean food improved the relative retentions of nitrogen, calcium and phosphorus. The modified soy bean food, from our observations, appears to be a satisfactory food for infants. It is concluded that in the feeding of infants the relative proportions of nitrogen, calcium and phosphorus in the diet are fully as important as the absolute intake of these elements. From the results of this study, it is suggested that, as the relative proportions of these elements in cows' milk allow adequate retention, this ratio seems a safe guide to follow."

From the foregoing it is seen that there is a definite relationship between calcium and other elements. Later will follow abstracts indicating the rôle played by the endocrine system in influencing this balance with special reference to the parathyroids. A paper entitled "The Effect of Calcium on the Storage of Colloid in the Thyroid Gland" suggests a reversed effect on another component of the endocrine system. Klein[5] made a series of studies on 36 young white rats. He introduces his presentation as follows: "For some time iodin has been emphasized as the most important factor in thyroid function. Iodin, however, is only one factor. Calcium is another element necessary to proper thyroid function. Various aspects of the problem have been discussed by Berry, Hellwig, Kottman, Abelin and Thompson. As the latter has stated, both calcium and iodin exert important influences on the thyroid, the normal function of which seems to depend on a proper relation between these two elements. Calcium in limestone areas has been stressed as an important factor in the causation of goiter, through a water supply rich in this element. More recently Hellwig has demonstrated that excess of calcium in the presence of iodin deficiency causes hyperplastic changes in the thyroid. The results of his investigations suggest again that normal thyroid function may depend on the conjoint action of calcium and iodin. The purpose of my study is to determine what influence calcium exerts in the storage of colloid in the thyroid, particularly in the presence of thyroglobulin as well as of an excess of iodin in the water supply. The investigation was begun as the result of an interesting clinical experience in which the administration of calcium exerted a definite curative effect in acute hyperthyroidism. This raised the question: What effect has calcium on the function and structure of the thyroid gland which gives it thera-

peutic properties in clinical hyperthyroidism?" He summarizes his results as follows: "Calcium either by mouth or hypodermically increases the amount of colloid in the thyroid gland in the rat in the presence of thyroglobulin and iodin. Intercurrent respiratory infection may cause a decrease of colloid storage and of hyperplasia. Even in these animals calcium increased the storage of colloid. The therapeutic action of calcium in hyperthyroidism may be due to this property of increasing colloid storage in the presence of an excess of thyroglobulin."

On the other side of the picture the parathyroid glands are a part of the mechanism concerned with calcium metabolism. Removal of these results in tetany, a clinical picture associated with low serum calcium concentration. Schelling and Goodman[6] treated 2 patients suffering from postoperative parathyroid tetany with low phosphorus diets. This procedure was based on the known relationship between serum calcium and serum phosphorus concentration. Studies were made of the effect of calcium, magnesium, parathyroid extract and vitamin D on the concentration of calcium and inorganic phosphorus in the serum and on the excretion of these substances in the urine. They state: "The advantages of the low phosphorus diet in the treatment of parathyroprivic tetany are as follows: (1) It prevents phosphorus retention and thereby allows the serum calcium to approach non-tetanic levels. (2) Less calcium is needed to rid the body of the retained phosphorus as the insoluble salt. (3) It minimizes or dispenses with the use of parathyroid extract in cases with marked phosphorus retention and thus reduces the possibility of metastatic calcification and renal impairment. (4) It obviates the use of vitamin D, since its administration in the presence of phosphorus retention may predispose to metastatic calcification. (5) The diet may be derived from a variety of food substances and thus eliminates the monotony of eating the same articles of food daily. (6) The treatment may be continued at home without inconveniencing the patient and without the need of too frequent analyses of the blood for calcium, as when parathyroid extract is used. Menus for low phosphorus diets may be easily calculated from tables given by Sherman and by Simmonds. The added calcium may be given as the lactate or the carbonate and the magnesium as the lactate, to prevent transient or permanent tetany, in renal rickets and in nephritis with phosphorus retention. The use of high calcium diets for the treatment of nephritis with phosphorus retention was previously suggested by Briggs."

Craig[7] introduces report of a case of tetany of the newborn by saying that the medical literature is rich in statements that tetany does not occur in the newborn. Many instances of convulsions in the newborn undoubtedly are cases of tetany. Perhaps many pediatricians and physicians have erred in the same manner as the Reviewer in failing to publish their cases of convulsions in the newborn responding favorably to the injection of calcium solutions. Craig says: "The striking factors in this case were the absence of marked tetanic symptoms, such as true spasticity and cardopedal spasm and the rapid response to calcium medication. I think that any newborn child having convulsions when the spinal fluid is negative should have the therapeutic test of calcium administration, regardless of the lack of the more classical signs and symptoms of so-called tetany. Certainly no harm can be done. The purpose of reporting this case is to emphasize that

convulsions in the first few days of life may not be due to birth hemorrhage, that the symptom complex, tetany of the newborn, does occur in the early days of life. Whenever there is doubt, the infant should be given the benefit of calcium medication."

Small[8] reports a case of tetany developing on the 9th day of life. His patient, at the age of 3 years and 9 months, had made normal mental and physical progress with no recurrence of the convulsions. His comment is quoted: "Benita Wolff quoted by Klose bases considerable importance on increase of irritability, and says, 'Chvostek sign is pathognomonic,' and does not accept a diagnosis without evidence of increased galvanic irritation. In the light of the work of Stevenson, Mitchell and Koch, who found in normal newborn infants from 12 hours to 21 days, that a Chvostek sign occurred consistently without serologic or electric evidences of tetany, also in view of the fact that the case herein reported as well as Power's case not showing a Chvostek sign, this sign is made of questionable importance. It certainly removes it from the category of 'pathognomonic signs.' At the present time the consensus of opinion favors the view that a lowered blood calcium is the pathognomonic sign of tetany, especially if other diseases in which a low serum calcium is present are excluded. What causes this lowering of blood calcium obviously is not clearly understood and has been the basis of considerable discussion. That there seems to be a sufficient storage of calcium elsewhere in the body is proved by the fact that a patient with tetany and a lowered blood calcium can be cured without additional calcium being given. Thus the administration of cod liver oil and viosterol as well as ultraviolet irradiation are agents which have been used successfully. Parathormone has also been used to raise the blood calcium to normal levels. Gamble and coworkers showed successful results with the use of acid-producing substances, such as hydrochloric acid, ammonium chlorid or calcium chlorid. There are several interesting facts brought out in this case study. First, that tetany may occur in bizarre form with only a few of the so-called conventional symptoms and signs. Secondly, the condition readily simulated birth injury, although a little late in onset of symptoms. Whether or not a relationship existed between the mother's mild toxemia or antecedent infection (Vincent's) and the baby's symptoms is speculative. It would seem likely that in view of the temperature an infection played some part in precipitating an attack, even though the nature of the infection was not demonstrated."

Wilder, Higgins and Sheard[9] studied the significance of the hypertrophy and hyperplasia of the parathyroids in rickets and osteomalacia by a series of experiments with chicks. Their conclusions are quoted: "Experiments with chicks reveal that deprivation of vitamin D, sufficient in degree to cause rickets, will produce hypertrophy and hyperplasia of the parathyroid glands; that the parenteral administration of parathormone in such minor degrees of deprivation of vitamin D prevents this hypertrophy and hyperplasia, but that when the deprivation of vitamin D is extreme, so that rickets is clearly in evidence, administering parathormone may restrict but will not prevent the hypertrophy and the hyperplasia of the glands. It appears from this and other evidence cited that the hypertrophy and hyperplasia of the parathyroid glands of chicks, under conditions of deficiency of vita-

min D, depend on their accelerated functional activity. Other observations are interpreted to mean that the supply of parathyroid hormone determines the sensitivity of the organism to the action of vitamin D. A diminished supply of the hormone, as after parathyroidectomy, diminishes the ability of the organism to function normally with restricted amount of vitamin D; an augmented supply conditions the tissues of the organism so that the effects of the vitamin are more intense, and so that amounts of the vitamin, which otherwise would not prevent rickets, do prevent rickets. By virtue of the capacity of the parathyroid glands to accelerate the rate of supply of their product, and owing to the resulting conditioning of the tissue (increased sensitivity to vitamin D), the organism is enabled to withstand periods of relative deficiency of vitamin D which otherwise would produce rickets or osteomalacia. This compensatory mechanism is adequate to protect against relative degrees of deficiency of vitamin D; it is inadequate, as would be expected, when deficiency of vitamin D is extreme." Excessive activity of the parathyroid results in a typical clinical picture.

Bauer[10] says: "Hyperparathyroidism or generalized osteitis fibrosa cystica is a clear-cut, distinct disease entity caused by an increased secretion of the parathyroid hormone. . . . All cases thus far reported have been due to a parathyroid adenoma. The fact that it is a disease of endocrine origin implies that the entire skeleton is affected. Arthritis and Paget's disease are never generalized skeletal diseases. This fact alone argues against their being of parathyroid origin. Hyperparathyroidism is a disease characterized by definite alterations in the calcium and phosphorus metabolism as well as by certain symptoms and signs. The alterations in the calcium and phosphorus metabolism are: (1) An elevated serum calcium. Serum calcium values as high as 23.6 mg. per 100 cc. have been reported. The normal serum calcium varies between 9.5 and 10.5 mg. (2) A decreased serum phosphorus. Values as low as 1.4 mg. per 100 cc. have been observed, in contrast to normal values of 4 to 5 mg. (3) An increased calcium excretion. The increased excretion of calcium is entirely urinary, the fecal excretion being unaffected. (4) An increased phosphorus excretion. The increased excretion of phosphorus is also entirely urinary. The increased excretions of calcium and phosphorus in 1 reported case were of the same magnitude as those in a normal individual receiving 100 units of an active parathyroid extract per day. These alterations in the calcium and phosphorus metabolism may be accompanied by any or all of the following symptoms and signs: (1) Polydipsia; (2) polyuria; (3) weakness and loss of strength; (4) constipation; (5) loss of appetite; (6) loss of weight; (7) indefinite muscle and joint aches and pains, commonly diagnosed rheumatism, arthritis or neuritis; (8) bone tenderness; (9) frequent fractures, often following slight trauma; (10) decreased excitability of the nerves; (11) skeletal shortening; (12) kyphosis; (13) bone tumors, frequently diagnosed epulis of the jaw or giant-cell tumor in other bones; (14) kidney or ureteral stones (usually bilateral); (15) characteristic Roentgen ray findings, such as generalized decalcification, bone tumors, multiple bone cysts, fish type vertebral bodies, etc.; (16) frequently anemia with leukopenia. In view of the above facts no patient should be subjected to a parathyroidectomy until sufficient evidence has been gathered from the history, physical examination, Roentgen examination and metabolism studies to leave no doubt as

to the correctness of the diagnosis of hyperparathyroidism. Until some simple test for hyperparathyroidism is devised, all suspected or questionable cases of hyperparathyroidism should be very carefully studied. Serum calcium and serum phosphorus determinations should be made and, if possible, serum phosphatase as well as total calcium and phosphorus metabolism studies. It certainly behooves us to proceed cautiously before making or accepting any statement which implies that certain cases of arthritis are due to hyperparathyroidism or that Paget's disease is of parathyroid origin. No findings have been seen that would suggest the existence of hyperparathyroidism as a causal factor. True, many of the cases of rheumatoid arthritis show Roentgen ray evidence of decalcification (bone atrophy). However, this is no more than we often see associated with disuse. Furthermore, we know that the calcium excretion of a patient when immobilized in a cast is much higher than when this same patient is allowed ordinary ward activity. The improvement reported in cases following parathyroidectomy may have been due to anesthesia, rest in bed, or a natural remission of the disease. These 3 factors are all capable of bringing about improvement, particularly in cases of rheumatoid arthritis. Because the latter disease is characterized by remissions and relapses, improvement is often ascribed to a particular form of therapy, whereas in reality it may represent nothing more than a natural remission."

During the past 2 or 3 years a number of contributions on the subject of hyperparathyroidism have appeared. A few of these are enumerated: Pemberton,[11] Schultzer,[12] Sainton,[13] Rankin and Priestley,[14] and Cohen and Kelly.[15] Under the title of "Parathyroid Tumors Without Osteitis Fibrosa," Hadfield and Rogers[16] report 2 tumors of the parathyroid gland. One occurred in a woman, aged 58, the other in a man, aged 51. The bulk of the tumors was relatively enormous. In 1 there appeared at first to be some reason for regarding the enlargement as being etiologically related to the skeletal changes of frank acromegaly, associated with a large chromophil adenoma of the pituitary. In the other an adenoma, indistinguishable as far as could be judged by ordinary histologic methods from those described in general osteitis fibrosa, was associated with a radiologically normal skeleton. The authors have been able to find only 6 previously reported cases of parathyroid adenoma or hyperplasia associated with pituitary disease. They do not think that this association is so rare as this figure indicates. They think that the skeletal overgrowth of acromegaly alone should, theoretically, make excessive demands on the parathyroids. After some argument they conclude that in the first of their 2 cases the adenomatous enlargement of the parathyroid was unrelated to the skeletal changes; in other words, they place it in the same category as their second case. They point out that since Mandl restored the calcium metabolism to normal in a case of osteitis fibrosa by excision of a parathyroid tumor, and thus disproved Erdheim's theory according to which the parathyroid adenomata in these cases were secondary to the disease of the skeleton, the publication of similar cases has given rise to the impression that a parathyroid adenoma must of necessity be associated with diffuse skeletal softening. They hold that their 2 cases prove this to be fallacious. In their opinion it seems likely that parathyroid tumor, closely resembling the normal gland, may occur without elaborating any excess of internal secretion.

REFERENCES.

1. Brown, A., and Tisdall, F. F.: Brit. Med. J., **1**, 55, 1933.
2. Daniels, A. L., Hutton, M. K., Knott, E., Everson, G., and Wright, O.: Am. J. Dis. Child., **47**, 499, 1934.
3. Jeans, P. C., and Stearns, G.: Ibid., **46**, 69, 1933.
4. Stearns, G.: Ibid., p. 7.
5. Klein, J.: Ann. Int. Med., **7**, 1080, 1934.
6. Schelling, D. H., and Goodman, M. J.: J. Am. Med. Assn., **102**, 669, 1934.
7. Craig, J. D.: J. Pediat., **4**, 219, 1934.
8. Small, A. S.: Ibid., **2**, 681, 1933.
9. Wilder, R. M., Higgins, G. M., and Sheard, C.: Ann. Int. Med., **7**, 1059, 1934.
10. Bauer, W.: J. Bone and Joint Surg., **15**, 135, 1933.
11. Pemberton, J. de J.: Minnesota Med., **15**, 729, 1932.
12. Schultzer, P.: Ugesk. f. Læger, **94**, 485, 1932.
13. Sainton, P.: J. méd. franç., **21**, 3, 1932.
14. Rankin, F. W., and Priestley, J. T.: Am. J. Surg., **20**, 298, 1933.
15. Cohen, H., and Kelly, R. E.: Brit. J. Surg., **20**, 472, 1933.
16. Hadfield, G., and Rogers, H.: J. Path. and Bact., **35**, 259, 1932.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 21, 1934

An Improved Colorimetric Method for Determining Sulphate in Serum and Urine Adaptable to the Determination of Sulphate Clearance.—T. V. Letonoff and J. G. Reinhold (Laboratories of Philadelphia General Hospital). Sodium-beta-naphthoquinone-4-sulphonate (Folin's amino-acid reagent) develops an intense and stable color with benzidin. The chromogenic power of this reaction is far greater than that of the unsatisfactory ferric chlorid-hydrogen peroxid reaction used by Wakefield in his modification of the Hubbard microsulphate method.[1] A procedure for the determination of sulphate in serum and urine has been developed utilizing the reaction of benzidin sulphate with the amino-acid reagent in the presence of a sodium borate-sodium hydroxid buffer. Acetone is added after the color reaction is completed to diminish the color of the reagent. An additional innovation for the determination of sulphate is the use of uranium acetate for the removal of proteins. This reagent removes phosphate as well, consequently error due to precipitation of benzidin by phosphate when increased concentrations of the latter are encountered is avoided. Determinations of sulphate in urine by the modified method agree closely with the results by Folin's gravimetric method. Recoveries of sulphate added to serum tended to be low, but were within limits permitting the use of the method for sulphate clearance determination.

The Prophylaxis of Anaphylaxis in the Actively Sensitized Guinea Pig.—A. H. Zifferblatt and H. K. Seelaus (Laboratory of Immunology, Philadelphia College of Pharmacy and Science). Guinea pigs actively

[1] Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, The Williams & Wilkins Company, vol. **2**, 1932.

sensitized with horse serum were protected from anaphylactic shock by treatment with an iodin solution. This solution was prepared by forcing iodin vapor into sterile distilled water by means of a pump. When completed, the solution contained 0.0079 gm. per cc. of the fluid, hydrogen-ion concentration 4.6, specific gravity 1.037. The treatment of previously sensitized animals consisted of intraperitoneal injections of 0.5 to 0.85 cc. of the solution until 10 or 12 cc. had been administered. Either of these amounts was found sufficient to desensitize the animal. Toxicity due to cumulative effect of the drug, used therapeutically, was not observed. The solution proved toxic in quantities of 2 cc. and 3 cc. in animals weighing 410 and 790 gm. respectively

The writers believe for the present that the iodin is assimilated by the cells chiefly affected in anaphylaxis and causes a change in their chemical constitution. This change induces an altered reaction capacity of the cell toward the specific antigen, thus conferring immunity on the animal to subsequent shock when the antigen is reinjected.

The Syneresis of Blood Clots: The Rôle Played by the Blood Platelets.—L. M. TOCANTINS (Department of Medicine, Jefferson Medical College). The dispute over the rôle, if any, that the platelets play in the syneresis of blood clots can be traced to differences in methods of counting platelets and of estimating syneresis, and to the ambiguous use of this term. A distinction should be drawn between spontaneous syneresis and that following artificial separation of the clot from the walls of the vessel. By a series of experiments consisting in the addition of antiplatelet serum and of intact and destroyed platelets from different animals, in various amounts, at different locations, to normal or deplateletized blood or recalcified oxalated plasma, the following conclusions were arrived at: (1) Spontaneous syneresis of blood clots is almost wholly a function of the blood platelet; (2) only the intact, undestroyed platelets can bring about spontaneous syneresis: (3) that property of the blood platelets is not species specific.

The Origin of the VIIth and VIIIth Cranial Ganglia in the Amphibian Embryo.—C. L. YNTEMA (Laboratory of Anatomy, University of Pennsylvania). The origin of the VIIth and VIIIth cranial ganglia was studied in the embryo of Amblystoma punctatum. The method used was to transplant ectoderm from an embryo which had been stained with Nile-blue sulphate to the orthotopic position on an unstained embryo. The stain in the granules was preserved in sections.

It was found that the different sources of the ganglia were separable. The neural crest made a small contribution which was situated in the roots of the VIIth and VIIIthe nerves. The remaining and greater part of the VIIth ganglion was derived from the pre-auditory placode and the hyomandibular epibranchial placode: the former contributed the anterolateral and ventrolateral ganglia; the latter, the facial ganglion. Aside from the small neural crest contribution, the VIIIth ganglion was derived from the otic vesicle.

The Conduction of Cortical Impulses to the Autonomic System.—E. A. SPIEGEL and W. C. HUNSICKER, JR. (Department of Experi-

mental Neurology, D. J. McCarthy Foundation, Temple University School of Medicine). The conduction of cortical impulses to vegetative organs was studied in 30 cats.

In the first series of experiments "extrapyramidal" fibers arising from the hypothalamus were severed. In a second series of experiments a transverse section of both pyramidal tracts was made. After the lesion on either of these systems had been performed, the effects of stimulation of the motor cortex and the frontal lobe was noted on the pupil, the bloodvessels, the sweat glands and the urinary bladder.

In both groups of experiments the cortical stimulation elicited reactions of the above-mentioned organs. It is, therefore, concluded that there exists a double (pyramidal and extrapyramidal) conduction of corticofugal impulses to the autonomic centers in the cord.

Vasomotor Reflexes in the Splanchnic Area.—G. D. GAMMON[1] and D. W. BRONK (Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania). Sensory zones concerned in the reflex control of blood pressure have been found in endings of nerves surrounding the vessels of the splanchnic areas. The most important factor conditioning the discharge of impulses appears to be the state of distention—hence the volume of blood—of the splanchnic vessels. The endings responsible are Pacinian corpuscles in the mesentery. Preliminary experiments tend to indicate that the nervous discharge set up by distension of the vessels effects a reflex contraction of the vessels in this region. Because of the significance of the splanchnic area in control of blood pressure the importance of this afferent mechanism is stressed.

[1] Godey Fellow in Medicine.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.